Methodology of clinical trials of adjuvant medical therapy in peripheral bypass surgery: A critical reappraisal following a large prospective trial

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METHODOLOGY OF CLINICAL TRIALS OF ADJUVANT MEDICAL THERAPY IN PERIPHERAL BYPASS SURGERY: A CRITICAL REAPPRAISAL FOLLOWING A LARGE PROSPECTIVE TRIAL

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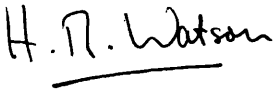

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Summary

Review of the literature on clinical trials of adjuvant medical therapy in peripheral bypass procedures indicated that there are many deficiencies in published trials, notably in the definition of patients and procedures, sample size, the definition of a primary endpoint and the availability of clinical outcome data. Consideration of the characteristics of patients studied was shown to be important in the interpretation of studies of antiplatelet agents.

A multicentre clinical trial was performed in order to determine the efficacy of iloprost, a prostacyclin analogue, in the maintenance of femorodistal bypass patency. The trial provided a database on 517 patients which included patient characteristics, the surgical procedures performed and a 12 month follow-up of bypass patency and clinical outcome.

The database was used to develop a score for comparing symptom severity in patients with severe leg ischaemia and then to investigate factors associated with outcome in terms of bypass patency, limb survival and patient survival. The clinical relevance of outcomes measured in terms of bypass patency and vascular surgical interventions were evaluated.

Intravenous iloprost was found to be ineffective in the maintenance of bypass patency when applied across the range of different procedures included in this trial. There was no convincing evidence of long-term efficacy in either vein or prosthetic grafts when analysed separately, although early graft occlusions in prosthetic grafts were less frequent in the iloprost group. Large differences between centres were found in patient selection, including some factors known to influence bypass patency or clinical outcomes. Overall clinical outcome was poor in the patients studied and was found to be less strongly associated with bypass patency than often thought. The need for reintervention was found to represent the clinical success of the initial bypass procedure better than an assessment of bypass patency.

Better designed studies are required in this indication. It is proposed that future studies should present clinical outcomes in addition to patency or reintervention results. Patients should be carefully characterised and results with different graft materials analysed separately.

1. BACKGROUND

1.1. Background, statement of objectives and structure of thesis

Background

The use of pharmacological agents in combination with peripheral bypass surgery to improve the outcome of the surgical procedures is not highly developed. Consequently, the optimal clinical trial methods have yet to be defined.

Objectives

The objectives of these investigations were to accomplish the following:

- Evaluate the standard of clinical trial design in the investigation of adjuvant medical therapy in peripheral bypass surgery and the current evidence for the use of such agents in the maintenance of peripheral bypass graft patency
- Describe a drug development programme for the maintenance of femorodistal bypass grafts
- Determine the efficacy of peri-operative iloprost in reducing distal bypass graft failure
- Investigate the extent and importance of intercentre differences in a multicentre trial in distal bypass procedures
- Investigate the relationship between bypass patency and clinical outcome after distal bypass surgery and to investigate alternative methods of expressing outcome after distal bypass surgery

Structure of the thesis

The introductory sections of the thesis divide the review of relevant literature into several sections. The thesis commences with a description of femorodistal bypass surgery and factors which may influence its outcome followed by a comprehensive literature review of controlled clinical trials in this field including a meta-analysis of trials with antiplatelet agents. The development of the prostacyclin analogue, iloprost, in a sequence of studies in this indication is then described. These sections are followed by a description of the methods used in performing the main trial with iloprost. The methods used in data collection and analysis of the treatment effect are described and the outcome of the trial.

The iloprost database was then used to investigate intercentre differences in patient selection and to evaluate the clinical relevance of bypass patency as a primary trial endpoint in this indication. An overall discussion and conclusions are presented at the end of the thesis.

2. INTRODUCTION

2.1. Femorodistal bypass surgery

Clinical Problem

Femorodistal bypass procedures are performed in cases of severe lower limb ischaemia resulting from peripheral arterial occlusive disease, usually when patients are suffering from pain at rest and ischaemic ulcers or gangrene. In many cases the operation is a last attempt to avoid amputation of the leg. Such long bypass procedures are seldom necessary in patients who have non-limb threatening intermittent claudication as their only symptom.

In the case of severe chronic ischaemia of the lower limb, the fundamental cause is atherosclerosis of the major arteries. The development of stenoses and occlusions in the proximal arteries, often with the additional involvement of thrombosis, severely reduces blood flow to the distal circulation. In the early stages of the disease, formation of collateral vessels may compensate for the reduced blood flow through the main arteries to supply the nutritive requirements of the tissues. The symptoms of severe ischaemia develop when the blood flow is impaired to the extent that this compensatory mechanism and other microvascular homeostatic mechanisms are insufficient to maintain nutritive microvascular blood flow. Lower limb ischaemia is thought to involve many changes in the microvasculature resulting from the reduced perfusion pressure. These may include failure of vessel tone autoregulation (Ubbink *et al* 1990), activation of platelets and white cells (d'Angelo *et al* 1978), fibrin formation and increased blood viscosity, and the formation and release of vasoactive mediators (e.g. TxA_2, 5-HT) which would accompany these other changes (Lowe *et al* 1990).

The consequences of the severe ischaemia are severe pain, ulcer formation and a threat to the survival of the leg. Pharmacotherapy other than pain relief with powerful analgesics has had some limited success in resolving symptoms (Dormandy 1994), but the treatment of choice remains intervention in the form of balloon catheter dilation of short lesions and bypass grafts in the case of more extensive disease.

Patients with severe atherosclerotic lesions in the arteries of the leg commonly also have coronary and cerebrovascular disease. Risk factors for atherosclerosis, such as hypertension, smoking, diabetes mellitus and hyperlipidaemia, are common and patients often have a history of myocardial infarction, stroke and other cardiovascular disease (Dormandy *et al* 1989). There is an increasing incidence of severe leg ischaemia with increasing age and the patient's general state of health and the likelihood of serious cardiovascular events have to be considered in the decision on the optimal treatment for the patient.

Pre-operative and intra-operative assessments

The presence of pain at rest, ulcers and gangrene are routinely documented before surgery, but not usually quantified. Intermittent claudication, however, is usually quantified by means of an exercise tolerance test. Clinical assessment of the patients before femorodistal bypass surgery also includes the investigating the presence of arterial pulses and the assessment of the systolic pressures in the arteries at the ankle, the anterior tibial and the dorsalis pedis, using Doppler ultrasound or strain-gauge techniques.

Prior to surgery, the patient's cardiological and pulmonary status is assessed to ensure that the patient is fit enough to undergo a lengthy surgical procedure. Specific assessments used in planning and preparing for a femorodistal bypass procedure include visualisation of the relevant arteries by conventional angiography or by digital subtraction angiography (DSA). The occlusions or stenoses in the arteries which are giving rise to the symptoms can be located and the appropriate procedure to bypass these segments planned. Angiography is usually performed before surgery, but may also be performed 'on table' at the during the operation. The status of the arteries of the leg may be recorded as simply patent or occluded, or may be quantified more precisely by the calculation of a run-off score. A number of different angiographic scoring systems have been devised. One which has been proposed for general use in order to standardise the assessment of patients is commonly known as the Rutherford score (Rutherford *et al* 1986).

At the end of the bypass procedure measurements of the flow through the graft may be made and calculations of distal resistance to flow can be performed, but this is not routine practice at most centres. Bypass quality and function is also checked intra-operatively using duplex ultrasound, angiography and occasionally by angioscopy.

Surgical procedures

The procedure involves bypassing stenosed or occluded sections of the femoral, popliteal and tibial arteries using a graft from one of the femoral arteries to one of the calf vessels. This involves using a relatively long graft of either autogenous vein or a prosthetic material and with the distal anastomosis to a relatively small artery.

The location of the proximal anastomosis is selected so as to provide the optimal inflow to the bypass graft. The common femoral artery is most often used, but the femoral bifurcation, the femoral profunda artery and the superficial femoral artery are also frequently used. Rarely used for the proximal anastomosis are the iliac artery and, at the distal extreme, the proximal section of the popliteal artery.

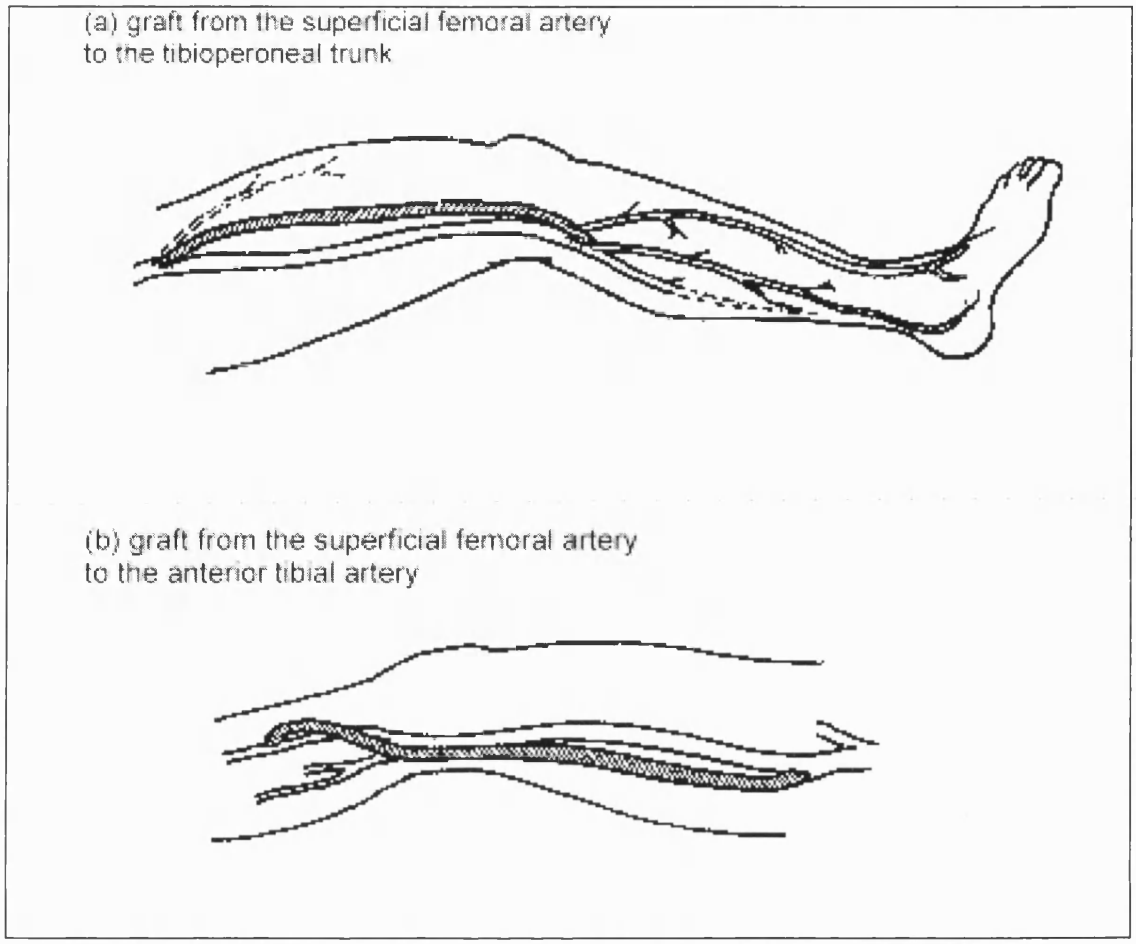
The distal anastomosis is usually to the tibioperoneal trunk, the anterior or posterior tibial artery or to the peroneal artery (Figure 1). More distal anastomoses to the pedal arteries have been reported, but are rarely performed in most centres. Femoropopliteal bypasses below the knee are also sometimes considered to be femorodistal grafts, but differ in that they frequently have better outflow through more than one calf vessel, and hence greater likelihood of success. The location of the distal anastomosis on the calf vessel is conventionally described as being in the upper, middle or lower third of the calf. The most proximal site feasible is chosen in order to avoid an unnecessarily long graft.

There are conflicting requirements to consider in the choice of location of the distal anastomosis. It is easier to anastomose to a larger artery and shorter grafts give better results than long ones and increase the likelihood that sufficient good quality autogenous vein will be available. This argues for a more proximally located distal anastomosis. On the other hand, it is essential that all areas of significant narrowing in the chosen artery are bypassed in order to ensure the best possible outflow from the graft. This will often lead to a more distal location being chosen despite the practical difficulties which this may entail.

The preferred graft material for femorodistal bypass procedures is autogenous saphenous vein. This has consistently been found to give superior patency rates to the prosthetic alternatives. There are two alternative techniques for using saphenous vein: the *in situ* technique and the reversed vein technique. Each has its advocates, but there is no consistent evidence that one is superior to the other (Harris *et al* 1993).

The *in situ* vein technique involves leaving the major part of the saphenous vein and its vasculature undisturbed while transposing the vein to the chosen arteries at each end. This has the advantage that the size of the vein corresponds well to the size of the artery at each anastomosis, but the disadvantage that it is necessary to destroy all the valves in the vein as they would act to impede flow. The reversed vein technique involves removing the chosen length of vein and reversing it so ensuring that the valves are no longer effective. The difficulty with this technique is that wider end of the vein has to be anastomosed to a small artery and the narrower end of the vein to a large artery. This is technically more challenging and is probably not haemodynamically ideal.

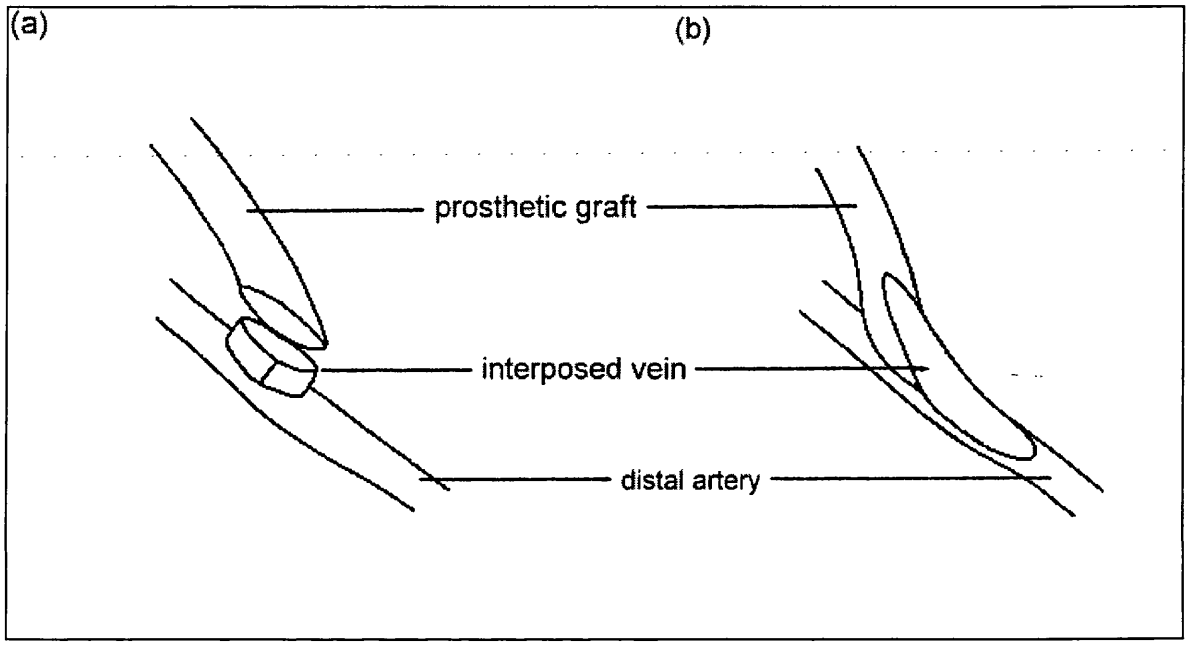
Figure 1. Examples of femorodistal bypass grafts



The first choice material for the graft is saphenous vein, but it is sometimes the case that the vein is of insufficient length or quality due to disease to be used as a conduit for a long bypass. In this event there are several other options. The cephalic or basilic vein may be taken from the arm, and sections of the saphenous or arm vein may be used sequentially to make a composite vein-vein graft or a segment of one of these veins may be used in combination with a length of prosthetic material, or a bypass wholly composed of a prosthetic material may be used. Other biological materials have also been tried, such as modified human umbilical vein, but with only limited success. Polytetrafluoroethylene (PTFE) is the prosthetic material of choice for these grafts, but grafts with a diameter of less than 4mm have a high likelihood of thrombosis. For this reason, when mixed vein and prosthetic material are used in sequence, it is always with the prosthetic section forming the upper part of the graft and the vein the more distal section with an anastomosis of prosthetic to vein in the middle. The smaller diameter vein

can then be used for the anastomosis with the smaller artery in the calf. The difference in compliance of prosthetic materials and arteries is also considered to be a drawback to the use of prosthetic grafts. This problem is currently tackled in one of two ways: interposition of a collar (or cuff) between the prosthetic graft and the artery and use of a vein patch to modify the shape and haemodynamics of the distal anastomosis (Figure 2).

Figure 2. Use of (a) a collar or (b) a patch at the distal anastomosis of a prosthetic graft



Additional surgical procedures may be performed concomitantly in order to improve the blood supply to the distal vascular bed. Femoral endarterectomy and profundaplasty may be indicated to improve inflow into the bypass graft if this is likely to be a limiting factor. Arteriovenous fistulae in the distal section of the graft are also performed in some centres with the aim of improving the volume flow through the graft, but with no proven benefit.

Both general anaesthesia and epidural anaesthesia are used frequently in patients undergoing distal bypass procedures. The choice may be dictated by the general policy of the centre or by specific considerations such as the patient's general state of health. Epidural anaesthesia theoretically produces vasodilation and therefore an increase in peripheral blood flow (Hickey *et al* 1995), but evidence for a benefit of this in terms of reduced early thrombosis following distal bypass is lacking (Schunn *et al* 1998). Local or regional anaesthesia may also be used occasionally.

Post-operative management

In the immediate post-operative period most patients will receive additional intravenous fluids in order to maintain perfusion pressure. These may consist of electrolyte or glucose solutions, dextrans, plasma and erythrocytes or whole blood transfusions when there has been appreciable blood loss. The use of intravenous fluids to improve perfusion pressure has always to be balanced against the risk of fluid overload in patients with impaired cardiac function. Additional analgesia over and above that which the patient was receiving for control of ischaemic rest pain may also be necessary in this period.

Heparin is usually given intra-operatively either systemically via the intravenous route or regionally by injection into the distal arterial circulation at the time that the arteries are clamped or shortly thereafter. Heparin anticoagulation may be neutralised at the end of the operation with protamine, but it is also common for heparinisation to be continued for the first day or two post-operatively. The drug may be given subcutaneously for a longer period as prophylaxis against venous thrombosis if the patient is not quickly mobile.

Oedema in the operated leg is frequently seen in the first two weeks after surgery and occasionally requires intervention such as fasciotomy. Wound infection can also occur and more seriously infection of the graft itself which is likely to prejudice its survival.

It is generally the policy to mobilise patients within a couple of days of surgery and it is not at all uncommon for them to leave hospital within a week. Patients at most centres will then be asked to return for regular follow-up which may include graft surveillance programmes using duplex ultrasound. These programmes aim to identify as early as possible grafts at risk of failing and to intervene before this occurs.

Outcome

The technical difficulty of these procedures together with graft thrombogenicity and a low volume flow through the graft due to the poor outflow and later development of stenoses produces a high failure rate in these procedures. Patency of femorodistal bypass grafts at one year has been reported in some series to be as low as 60% for vein grafts and 40% for prosthetic grafts. Higher patency rates up to 90% have also been reported and results appear to vary considerably depending on factors such as patient selection, preferred operation techniques and importantly the skill and experience of the surgeon.

The causes of bypass failure vary with time and graft material. Immediate occlusion of the graft occurring in the first 24-48 hours after surgery may be due to imperfections in surgical technique or a failure to establish an adequate blood flow

through the graft after release of the arterial clamps. Failure to establish an adequate blood flow might be a result of poor inflow, poor outflow or increased blood viscosity. In the first few weeks post-operatively bypass failure is likely to be due to graft thrombogenicity or increased blood viscosity, and after the first month the development of graft stenosis due to fibrous neointimal hyperplasia becomes a major contributing factor to failure. In the longer term, after 12 months, progression of atherosclerosis can also lead to bypass failure.

In about half of the cases in which the bypass occludes and is not reopened, the patient will require a major amputation. In some patients symptoms of ischaemia may return, but not with sufficient severity to warrant amputation and other patients may continue to be symptom-free for a while if the bypass had functioned for long enough to permit resolution of the original symptoms.

Post-operative assessment

Assessment of the patients after surgery is concerned with the technical success of the bypass procedure and the effect of surgery on the patient's symptoms. Technical success is recorded both in terms of the patency of the bypass graft and measurements of blood pressure and flow in the lower leg.

Bypass patency is described as (1) primary, if patency has been uninterrupted since the bypass graft was performed and no further procedures in the relevant segment have been necessary, (2) assisted primary, if the graft has not occluded, but a further intervention or surgical procedure was performed in order to ensure continued patency, or (3) secondary, if the bypass graft has occluded and been reopened. Patency may be assessed by ankle systolic blood pressure or by presence arterial pulses, but is more reliably confirmed by angiography or by duplex ultrasound measurement of blood flow velocity through the graft.

A successful bypass should improve blood flow to the tissues distal to the graft. This can be assessed by blood pressure measurements at the ankle usually using the Doppler technique. These are commonly expressed as the systolic ankle pressure or the ankle-brachial pressure index (ABPI), which is the ratio of the systolic pressure at the ankle to that measured in the brachial artery. Different pressure readings may be obtained from different vessels at the ankle, and in this event the highest pressure obtained would be quoted or used for calculation of the ABPI.

The status of the graft can also be assessed post-operatively by duplex scanning over the length of the graft. By identifying changes in flow velocity, this enables the detection of stenoses in the graft, which may develop, particularly in vein grafts over the

first year or two and threaten the viability of the graft in the long-term. Scanning is usually performed at regular intervals between one month and 12 months after the operation.

The clinical outcome of bypass surgery is routinely judged by changes in the symptoms of ischaemia at rest (pain and trophic lesions) and exercise capacity and by the avoidance of amputations in the relevant leg.

2.2. Considerations for clinical trials in peripheral bypass surgery

Describing symptom severity

Clinical trials in peripheral bypass surgery frequently include patients with diverse symptoms of ischaemia: rest pain, ulcers and gangrene. In the iloprost trial, as in other trials, various parameters - pain, analgesic use, presence of ulcers and gangrene - were documented separately. The comparison of overall symptom severity in different patient groups taking into account the various parameters is therefore difficult. The importance of this is that symptom and disease severity may be associated with outcome. A single symptom severity score would be an helpful, if it could be shown to be meaningful. Association of such a symptom score with patient outcome would be an indication that it was a good representation of disease severity.

There is currently no agreed standard for the documenting of patients' symptoms in severe lower limb ischaemia. Proposals have been put forward for classifying patients' symptoms in clinical trials (Rutherford *et al* 1986, Belch *et al* 1991), but these have not been widely adopted by authors of clinical trial reports and patients are often classified very simply into the four stages of peripheral arterial occlusive disease according to Fontaine (Table 1).

Table 1. Classification of peripheral arterial occlusive disease according to Fontaine

Stage	Description
1	arteriosclerotic lesions without clinical symptoms
2	claudication, no symptoms at rest
3	claudication, pain at rest
4	ulcers and/or gangrene

The scheme for classifying chronic limb ischaemia put forward by Rutherford *et al* (1986) is not a pure symptomatic classification, but also incorporates objective criteria based on treadmill and haemodynamic tests (Table 2).

Table 2. Clinical categories of chronic limb ischaemia according to Rutherford (1986)

Grade	Category	Clinical description	Objective criteria
0	0	• Asymptomatic - no haemodynamically significant disease.	• Normal treadmill/stress test
I	1	• Mild claudication	• Completes treadmill exercise; AP after exercise <50mmHg, but >25mmHg less than BP.
	2	• Moderate claudication	• Between categories 1 and 3.
	3	• Severe claudication	• Cannot complete treadmill exercise and AP after exercise <50mmHg.
II	4	• Ischaemic rest pain	• Resting AP<40mmHg, flat or barely pulsatile ankle or meta-tarsal PVR; TP<40mmHg.
III	5	• Minor tissue loss - non-healing ulcer, focal gangrene with diffuse pedal ischaemia.	• Resting AP<60mmHg, ankle or metatarsal PVR flat or barely pulsatile; TP<40mmHg.
	6	• Major tissue loss - extending above TM level, functional foot no longer salvageable.	• Same as category 5.

The scheme for scoring symptoms put forward by Belch *et al* (1991) assesses ulcers and gangrene each by three different parameters (Table 3) and the intensity of pain in terms of its affect on daily activities (Table 4). The scheme is very sophisticated in its detail, but requires subjective judgements on the part of the clinician and the patient.

Table 3. Scoring of ulcers and gangrene by Belch *et al* (1991)

ULCER	Score	GANGRENE
Ulcer base		***Stage of gangrene***
bone visible	1	gangrene with osteonecrosis or osteomyelitis
greasy	2	congestion of secretions, pockets of pus
fibrin layer	3	tendency to progress
clean, but not healing	4	tendency to remit
clean and healing	5	new vessel injection at edge
healed	6	healed,/demarcation/casting off
Extension of granulation		***Extension of gangrene***
low	0	forefoot, heel
medium	2	several toes
good	4	one toe
ulcer edge		***Classification of gangrene***
hard, thickened	0	moist gangrene
raised	2	mummification
soft	4	pregangrene

Table 4. Scoring of pain by Belch *et al* (1991) - rating scale from impression over whole day

Score	Description of pain
0	Pain present, cannot be ignored, rest or bed-rest required
1	Pain present, cannot be ignored, interferes with all tasks except taking care of basic needs (eating, toilet visits)
2	Pain present, cannot be ignored, interferes with concentration
3	Pain present, cannot be ignored, but does not interfere with everyday activities
4	Pain present, but can easily be ignored
5	No pain

Alternatives such as the use of visual analogue scales for the assessment of pain have been advocated (Heidrich *et al* 1995), but these also require a subjective judgement by the patient. The ideal for comparing symptom severity in different patient groups, either within a study or between studies, would be a scoring system which took into account the different types of symptom, pain and trophic lesions and their severity, and combined these into a single numerical value. Other desirable attributes of such a system would be to avoid the need for subjective patient or clinician judgements, to be simple to apply and to use unambiguous descriptions of categories which could be easily translated into different languages. Finally, there is a need for a symptom score which has some relevance for the clinical outcome in a patient.

Factors influencing patency

There is an extensive literature on factors associated with the outcome of peripheral bypass surgery. The majority of studies reported have included less than 500 patients and been conducted in single centres. There have been few such investigations exclusively in femorodistal bypass grafts, the majority of such studies including all infra-inguinal bypasses.

Studies including above- and below-knee grafts have typically found that the level of the graft is an important determinant of outcome both in studies including a mixture of graft materials (Budd *et al* 1990) and in vein grafts alone (Bergamini *et al* 1991). However, Tordoir *et al* (1993) also reported that the vessel and site of anastomosis was not associated with patency in a smaller series of distal grafts. There are theoretical reasons for thinking that the level of the distal anastomosis and length of graft would be of greater importance in prosthetic grafts.

Prospective randomised trials comparing autogenous vein and prosthetic grafts have found significantly better patency with vein in all femoropopliteal bypasses (Tilanus

et al 1985) and in below-knee grafts (Veith *et al* 1986), although the latter study did not show any difference between the materials in the first two years of a four year follow-up. Another series also showed a significant difference between vein and prosthetic grafts, but not in the first 12 months (Ameli *et al* 1988).

Several randomised studies have investigated, but failed to show any difference between the patency rates obtained with the *in situ* and the reversed techniques (Harris *et al* 1993, Watelet *et al* 1997). A recent large series of femoropopliteal and femorocrural grafts found a superiority after 12 months in primary patency of reversed vein compared to *in situ* vein grafts (Lawson *et al* 1999). However, this series did not involve a randomised assignment of technique and the safest conclusion seems to be that at least the reversed technique is no worse than the *in situ*.

Another aspect of the choice of graft material is the diameter of the vein used. This was associated with patency in a report of infrapopliteal bypasses (Wengerter *et al* 1990), but not significantly so in a study of above- and below-knee bypasses (Bergamini *et al* 1991), suggesting that this factor may be more important in distal bypass grafts.

The severity of the patients' arterial disease pre-operatively is generally not found to be predictive of bypass patency at 12 months, whether assessed in terms of symptoms or arterial pressures. However, there is an exception with two reports on studies which included patients with claudication as well as those with severe limb ischaemia. In these studies low ankle pressure and presence of gangrene were associated with poorer patency (Woodburn *et al* 1996) and claudicants had a superior patency to those undergoing bypass surgery for limb salvage (Belkin *et al* 1995). Angiographic assessments of run-off have been associated with long-term patency in earlier studies (Budd *et al* 1990, Woodburn *et al* 1996), but were not associated in a study restricted to CLI patients undergoing distal bypasses with a mean follow-up of 18 months (Tordoir *et al* 1993).

A pre-operative characteristic of the patients often associated with patency is patient gender. This has been reported, though not explained, in previous studies of peripheral bypasses (Ramsburgh *et al* 1977, Magnant *et al* 1993, Enzler *et al* 1994, Woodburn *et al* 1996, Luther *et al* 1997), although one study has also reported the opposite finding (Shah *et al* 1988) and one study has reported no difference (Harris *et al* 1993). Studies of patients undergoing coronary artery bypass grafting (CABG) have reported similar sex-related differences in bypass patency (Tyras *et al* 1978, Douglas *et al* 1981) and in operative mortality (Edwards *et al* 1998), although one study found the incidence of repeat revascularisation greater in women after CABG, but lower in women after percutaneous coronary angioplasty (Jacobs *et al* 1998). It has been postulated that

sex-related differences in the outcome of CABG might be a result of smaller blood vessels in females (Magnant *et al* 1993). The association of vessel size with gender in coronary bypass has been documented (Tyras *et al* 1978), but no data has been reported on the association of vessel size with gender to explain the outcome of peripheral reconstructions. Single centre studies have, however, reported an association of vein diameter with the patency of reversed vein grafts (Wengerter *et al* 1990) and of *in situ* vein grafts (Towne *et al* 1991). These results were reproduced in a prospective study with a longer follow-up of five years (Moody *et al* 1992). However, Wengerter *et al* (1990) failed to find any association of vein diameter with gender. A possible explanation for the difference in patencies is a poorer quality of vein conduit available in women. This would be consistent with the known higher incidence of venous disease in women (Callam 1996).

Few other pre-operative characteristics of the patients are consistently shown to be associated with bypass patency. Smoking is usually not associated with patency (Woodburn *et al* 1996, Bergamini *et al* 1991), but this is in contrast to a report of patients undergoing difficult distal bypasses (Rutherford *et al* 1988). Age is generally not associated with patency (Luther *et al* 1997), an exception being the series of Woodburn *et al* (1996). The usual lack of association of outcome with age may be attributable to the selection of patients well enough to undergo surgery.

Diabetic patients have more distal atherosclerosis (Rosenblatt *et al* 1990, Menzoian et al 1989) and have been reported to fare worse clinically after peripheral bypass grafting compared to non-diabetics (Rosenblatt *et al* 1990, Fowl *et al* 1989), but the literature does not support a poorer graft patency in diabetic patients. No influence of diabetes on patency in vein grafts was reported in three large series of patients mostly with CLI and tibial grafts (Bergamini *et al* 1991, Hurley *et al* 1987, Jensen *et al* 1992), although a poorer patency in diabetic women mostly with vein grafts has also been reported (Luther *et al* 1997). In contrast, another study found a superior patency with diabetic patients in vein grafts (Rutherford *et al* 1988). This may also be a consequence of patient selection, diabetic patients with poorer distal arterial run-off being excluded from surgery due to a poorer prognosis.

Factors influencing clinical outcome

In contrast to bypass patency, limb survival has been associated with disease severity. Fontaine stage, representing the severity of symptoms, has been found to be associated with the major amputation rate (Dietzek *et al* 1990, Fowl *et al* 1989) and patient survival (Rafferty *et al* 1987, DeWeese *et al* 1977). Thus disease severity may be more important

in determining clinical outcome than the technical outcome of distal bypass surgery. Diabetes mellitus has previously been reported to be associated with increased mortality (Kalman *et al* 1997) and not associated with major amputations in infra-inguinal vein bypass procedures (Jensen *et al* 1992, Hurley *et al* 1987). Other authors, however, have reported a higher amputation rate in diabetic patients (Kantonen *et al* 1998, Rosenblatt *et al* 1990, Rutherford *et al* 1988).

As in bypass patency, female gender has been found to be associated with a poorer limb survival in a study of infra-inguinal grafts (Woodburn *et al* 1996), which found a poorer outcome in women. The same study also reported associations of a good clinical outcome with aspirin use.

Intercentre differences

Published results in peripheral bypass surgery from individual surgical centres show considerable variation in the results of femorodistal bypass surgery (Wyatt *et al* 1995). The individual experience of the surgeon may be important, but other more easily quantifiable factors, such as characteristics of the patients selected for surgery, may also play a part. The same factors may give rise to differences in results between centres in a multicentre trial.

The skill of the individual surgeon may be one of the most important factors in the outcome of distal bypass surgery, but it is difficult to measure. One indicator of this might be the number of such procedures entered into a study during a fixed recruitment period. It might be expected that this would be roughly proportional to the number of procedures performed by the surgeon and his recent experience. Data from the Finnish national vascular registry indicate that the short term amputation rate was lower in centres performing more operations for critical leg ischaemia (Kantonen *et al* 1998). However, a survey from the United Kingdom found that centres performing more procedures did not have a better success rate (Vascular Surgical Society of Great Britain and Ireland 1995). An explanation for greater numbers of patients not being associated with better technical and clinical outcomes may be that centres performing fewer such procedures are often selecting only those patients with the greatest chance of benefiting from the operation (Wyatt *et al* 1995). The number of procedures performed may therefore not on its own be a good indication of a centre's likely success rate.

Centre differences can play a role within studies in this indication as few surgical centres perform a sufficient number of many types of peripheral bypass procedure to be able to complete a well powered study in a reasonable period of time

without cooperating with other centres. There is a need then to establish a common protocol which may be difficult without compromising a surgeon's ability to follow his instincts and experience in the individual case.

Graft surveillance

A major contributor to the failure of distal bypass grafts is the development of neointimal hyperplasia resulting in stenosis of the graft. This reduces the luminal diameter and volume of blood flow through the graft, threatening the improvement in clinical symptoms and increasing the likelihood of thrombotic occlusion of the graft. Vein graft stenosis was first reported by Szilagyi *et al* (1973) and duplex scanning of grafts as a means of detecting stenoses early was reported by Bandyk *et al* (1985) in a series of *in situ* saphenous vein grafts and by Mills *et al* (1990) in reversed saphenous vein grafts.

The incidence of vein graft stenoses after distal bypass grafting has been reported to range from 14% (Tønnesen *et al* 1998) to 46% (Brennan *et al* 1991). Duplex ultrasound equipment necessary for scanning vein grafts along their entire length for stenoses has become standard in most departments performing femorodistal bypass procedures, but vein graft surveillance is not routine at all hospitals and its regular application is dependent on the willingness of patients to return for regular follow-up to a department where this facility is available.

Differences in reported incidence of stenoses may arise from differences in scanning techniques, different definitions of a haemodynamically significant lesion as well as differences between centres in their choice of surgical techniques and the type of procedures performed. Since the definition of what is considered a haemodynamically significant stenosis is sometimes not stated in publications, the importance of this as a cause of the disparity between results from different centres is difficult to assess.

There are relatively few reports in the literature of stenoses in prosthetic grafts. Although stenoses are known to occur at the anastomotic sites of prosthetic grafts (Sottiurai 1990), the value of scanning prosthetic grafts is disputed. It has been reported to be ineffective (Lalak *et al* 1994) and not useful in improving prosthetic bypass patency (Lundell *et al* 1995), but a recent study has reported that velocity gradients from duplex scanning are useful for the detection of failing prosthetic grafts (Mawatari *et al* 1998).

The site of the stenosis varies. In a review of fifteen studies it was reported that the distal anastomosis was the least common site of stenosis, in 19% of stenosis cases when all of the different series were combined (Golledge *et al* 1996), although two of the studies included in the review did report a majority of stenoses in the distal portion of the graft (Thompson *et al* 1989, London *et al* 1993). The origin of stenosis in grafts is not

known. Trauma due to surgical clamping and valve disruption have been proposed, but the location of the stenoses and the similarity of stenosis rates with the *in situ* and the reversed vein techniques do not support of either of these hypotheses as the sole cause of stenosis. The majority of patients have only single stenoses suggesting that local factors are more important than the general condition of the patient (Berkowitz *et al* 1981, Bandyk *et al* 1987, Moody *et al* 1992).

Vein quality may be an important factor in the origin of graft stenoses. Pre-existing abnormalities could explain the focal nature of graft neointimal hyperplasia (Panetta *et al* 1992), and the use of composite vein-vein grafts in patients with poor quality veins could explain the higher incidence of stenoses reported after these procedures (Tønnesen *et al* 1998).

The regular surveillance of grafts allows remedial action to be taken, usually in the form of a percutaneous intervention, and has been advocated as a means of reducing the number of bypasses occluding and obtaining a higher patency rate in the long term (Moody *et al* 1990, London *et al* 1993). The value of dilatation of vein graft stenoses by angioplasty to improve patency rates is supported by a literature review (Golledge *et al* 1996) and by a randomised study comparing routine with intensive vein graft surveillance (Bergqvist *et al* 1996), although no improvement in limb salvage has been demonstrated. The decision whether or not to intervene on detection of a stenosis will depend on the degree of stenosis. A velocity ratio of 2.0 is often used as the definition of a significant stenosis, but evidence has been presented recently for intervention not being necessary as long as the velocity ratio is below 3.0 (Olojugba *et al* 1998). Indeed over forty percent of the grafts stenoses reported in that study resolved without intervention.

Summary

It is clear that performing and interpreting studies in peripheral bypass surgery presents a number of challenges: ensuring comparability of patient groups in terms of disease severity, ensuring that the results have not been prejudiced by imbalance in any of the clinical factors which may influence outcome or by intercentre differences in a multicentre study.

2.3. Adjuvant medical therapy in peripheral bypass surgery: A critical review of the methods and results of published clinical trials

Introduction

Infra-inguinal bypass surgery is performed for the relief of disabling intermittent claudication, ischaemic rest pain and trophic lesions. Areas of severe stenosis or occlusion are bypassed with grafts from the iliac or femoral arteries to the more distal femoral, popliteal or tibial vessels. The more distal the procedure, the more technically difficult the operation, due to the smaller arterial diameter, and the higher the risk of failure. As techniques have improved, distal procedures have become more common with the aim not only of relieving symptoms, but of avoiding amputation. Many bypass grafts are now performed to the below-knee popliteal or tibial arteries.

These below-knee grafts often suffer from a high resistance to outflow due to the size and state of the distal arteries. Combined with the greater technical problems encountered with anastomoses to small arteries and obtaining sufficient length of good quality vein this leads to a lower success rate with femorodistal grafts than with femoropopliteal grafts. The European Consensus Document on Chronic Critical Leg Ischaemia (European Working Group on Critical Leg Ischaemia 1991) quotes one year patency rates of 75% for above-knee femoropopliteal, 70% for below-knee femoropopliteal and 70% for femorotibial grafts with autogenous vein. With prosthetic grafts the respective figures were reported to be 65%, 60% and 40% at one year.

The causes of bypass failure vary with time and graft material. Immediate occlusion of the graft occurring in the first 24 - 48 hours after surgery may be due to imperfections in surgical technique (Stept *et al* 1987) or a failure to establish an adequate blood flow through the graft after release of the arterial clamps. Failure to establish an adequate blood flow might be a result of poor inflow or poor outflow. Thrombogenicity of graft materials is an important cause of failure in prosthetic grafts (Hanson *et al* 1987) and after the first month the development of graft stenosis due to fibrous neointimal hyperplasia becomes a major contributing factor to occlusion, particularly in vein grafts (Bandyk *et al* 1987). In the longer term, progression of atherosclerosis can also lead to bypass failure (Fuchs *et al* 1978).

Medical therapy used for the prevention of peripheral bypass failure has been reviewed by Lindblad *et al* (1995) and shown to vary from country to country. This suggests that the preference for one treatment over another is not based upon objective scientific evidence. One reason for this is the relative paucity of published material. Perhaps also for this reason, results of the use of oral medications after coronary artery bypass grafting have been extrapolated to use after peripheral bypass grafting. This applies particularly to the use of antithrombotic medications. A meta-analysis of

randomised controlled trials of platelet inhibitors to prevent occlusion of coronary artery bypass grafts showed a 41% relative reduction in graft occlusion (Antiplatelet Trialists' Collaboration 1994b). Although there are similarities in the two situations, the differences in surgical techniques, haemodynamics, duration of blood exposure to graft surfaces and the use of prosthetic materials in peripheral grafts suggest that it would be unwise to draw too many conclusions about the value of adjuvant therapy in peripheral bypass from results in coronary artery bypass studies (Clagett, 1988).

The purpose of this review is to investigate the strength of the evidence for the use of various agents which have been tested as adjuvant therapy in infra-inguinal bypass procedures. Some of the studies included were reported after the initiation of the trial presented in this thesis. A comparison of the standards in these trials versus those in published previously was also made. Trials of iloprost initiated and designed by the author were excluded from this review as they are summarised in the next chapter.

Methods

Published studies were identified from computer databases (MEDLINE, EMBASE) and by manual searches. Initial key terms employed were: antiplatelet, anticoagulant, antithrombotic, peripheral bypass graft, vascular reconstruction, peripheral vascular disease, occlusion, clinical trial. Subsequently the names of agents tested in trials identified initially were used as keywords for searches of further trials with these agents.

All identified comparative clinical studies of adjuvant pharmacological therapy during or after infra-inguinal bypass surgery are included provided that technical or clinical success was reported. Studies reporting only surrogate endpoints, such as platelet uptake, were excluded, as were those without any comparator group. Features of the trial designs and methods were reviewed and the findings for each treatment were summarised based on the soundness of the experimental design.

Meta-analysis

A formal meta-analysis was performed of the trials with the most frequently tested agents, platelet inhibitors acting on the cyclo-oxygenase enzyme, in order to investigate the possible sources of heterogeneity in the results. For each trial included in the meta-analysis, the reported absolute difference in the percentage of bypasses patent at the end of follow-up was identified (active treatment patency rate - placebo patency rate) together with its standard error. Where a trial involved more than one active treatment arm this

difference was calculated for each active treatment. Graphical displays were then used to identify which of the following appeared to be correlated with the magnitude of treatment benefit: treatment regimen being tested, duration of follow-up, trial size, type of bypass materials, level of bypass, severity of ischaemia and proportion of smokers.

Bypass materials were classified as vein or prosthetic, with composite vein-prosthetic grafts being classified as prosthetic. The level of bypass was classified as below-knee or above-knee. The severity of ischaemia was classified as either intermittent claudication or more severe ischaemia characterised by pain at rest with or without ulcers. Trial size was included to investigate the possibility of reporting bias. As some of the trials involved more than one treatment comparison, trial size for each comparison was taken to be the number of patients in the smaller treatment group. This approximates the amount of information available and is adequate for the graphical analysis.

Relationships which appeared to be of interest were then investigated further using a multiple logistic regression analysis. The data were pooled over all trials for a fixed effects analysis. The basic 'unit' was the treatment group and all models fitted included factors identifying both trial and drug, whether singly or in combination. Where the value of a particular covariate was only known for a trial as a whole, it was assumed that the value applied equally to each treatment group in that trial. Mean results are quoted with standard deviations.

Results

The findings of this review are divided into three sections: the first section looks at general aspects of study methods and design, the second section reviews the methods and results reported by drug or class of drug and the third section deals with a meta-analysis of the platelet inhibitor trials.

Review of study methods

A total of 38 publications based on 29 studies were identified dealing with the question of adjuvant therapy in infra-inguinal bypass surgery (Table 5). The trials can be broadly divided into two types: (1) long-term anti-thrombotic treatment started pre- or post-operatively and continued until the end of the study follow-up and (2) peri-operative or early post-operative treatment for a limited period aimed at reducing early postoperative graft failure (up to the time of discharge). The first type includes all but two of the trials of antiplatelet agents such as aspirin and most of the trials of anticoagulants (coumarins and low molecular weight heparins (LMWH)). The second type includes the trials of dextran

40 and the prostaglandin E_1, which possess a number of properties suitable for the reduction of early graft failure.

Table 5. Treatments and number of comparative studies published

Drugs	**No. of studies**	**No. of publications**
Aspirin (± dipyridamole)	14	16
Ticlopidine	2	3
Other platelet inhibitors	4	4
Oral anticoagulants	5	10
Low molecular weight heparin	3	3
Dextran 40	4	4
Prostaglandin E_1	2	3

Patients and surgical procedures

The frequencies with which various criteria for selecting the trial patients were reported are given in Table 6. The principal criteria for selection of patients for the studies were usually the localisation of arterial disease and the procedure which the patients were undergoing. However, there were eight studies in which all infra-inguinal bypass procedures were included regardless of the vessels of origin and insertion and five of them did not report results of the different types of bypass procedures separately. In general the majority of bypasses reported were classified as femoropopliteal (Table 7). Three studies were exclusively concerned with below-knee femoropopliteal and femorotibial grafts and a further four studies analysed results of them separately. These grafts have a higher early postoperative failure rate and four of these six studies were trials of short-term peri-operative treatment.

Table 6. Criteria employed either in patient selection or for performing a separate analysis

Criteria for defining patients	**Frequency (n=29)**
Localisation of procedure	22
Bypass material	17
Severity of ischaemia	5
Poor angiographic run-off	2

Table 7. Selection of patients according to localisation of procedure

Type of procedures (by location) included in trial	**Frequency (n=29)**
Trials including any infra-inguinal grafts	8
Trials including only femoropopliteal grafts	18
Trials including only below-knee femoropopliteal or tibial grafts	3

Bypass material was sometimes an additional criterion for entry into the study or the basis for separate analysis: vein grafts in eleven studies and prosthetic grafts in seven studies. Approximately half of the studies, however, contained a mixture of vein and prosthetic grafts with the results in most cases not being reported separately. The severity of ischaemic symptoms although usually described was seldom stated as a criterion for entry into the study.

Four studies attempted to define higher risk patients by the presence of rest pain or trophic lesions and only one study was found in which exclusively patients with intermittent claudication were included. Other studies additionally defined patients with a higher risk of graft failure by poor run-off, assessed angiographically (Rutherford *et al* 1984), or with a suboptimal venous conduit or those undergoing redo bypass procedures (Sarac *et al* 1998).

Study design

The design characteristics of the studies are described in Table 8. All but two of them were prospectively planned studies. The exceptions were comparisons with historical controls. Less than half of the studies involved a comparison with a placebo treated group and were performed in a double-blind fashion and only one of the seven studies comparing two active treatments was double-blind. There was no evidence that the use of a double-blind design for trials in this indication is increasing, as the median year of publication of open and double-blind studies identified was the same. The allocation of patients to treatment group was described as randomised in all prospective studies, but descriptions of the randomisation procedures used were lacking.

Table 8. Study designs

Design features		**No. of studies (n=29)**
Prospective recruitment		27
Comparator:	non-treated group	12
	placebo	10
	active comparator	7
Double-blind:		11
Randomised:		27

Study endpoints

The patency of a bypass graft can be described as primary, if no subsequent interventions have been performed to improve or recover graft function, assisted primary if the graft has not occluded, but an intervention has been performed to improve graft function, or secondary if the graft has occluded, but has been re-opened by subsequent intervention. All but one of the studies reported graft patency (or conversely graft occlusions) as an efficacy variable. This appeared to be primary graft patency in every case, but was unambiguously described as such in only seven of the 27 studies. Immediate postoperative graft occlusions were sometimes considered to be surgical rather than treatment failures and were excluded from the analysis in nine studies or excluded from the study by postoperative randomisation of patients with patent grafts.

Assisted primary patency was reported in two studies, in one of which it was the primary endpoint (Katz *et al* 1998), and secondary patency was explicitly reported only five times.

Although graft patency was the main study endpoint in 97% of the trials, the criteria for determining patency were not always clearly defined. Angiography 14%, duplex ultrasound 24%, Doppler pressures 62%, arterial pulses 41% and clinical symptoms 55% were used routinely either individually or in combination at follow-up to determine graft patency. Angiography or duplex ultrasound were additionally used in 48% of studies in order to confirm a suspected occlusion of the graft determined by other methods. In almost all trials more than one technique was used. One trial reported the review of all records concerning graft patency by a blinded validation committee (Becquemin 1997). In 21% of trials no methods were described for the determination of patency.

Limb survival rates (or conversely amputations) were reported in five studies and patient survival in 15 studies. Since these patients usually have widespread vascular disease, incidence of all major cardiovascular events is of interest and was also reported in five studies. The outcome in terms of intermittent claudication, ischaemic rest pain and trophic lesions was also mentioned in only four studies, although these symptoms were the reason for undertaking the bypass operation.

Duration of follow-up

It is frequently a feature of the follow-up of patients after arterial reconstructions that the period of observation is not uniform in all patients. In 66% of studies follow-up was performed for at least 12 months in at least a proportion of the patients.

The duration of follow-up was standardised for all patients in less than half of the studies and was 12 months in the majority of these cases (range 6 months to 60 months). In other studies results were reported as Kaplan-Meier plots or life-table analysis with follow-up of variable duration within each study. The range of follow-up duration within studies was sometimes as great as 2 to 5 years and the mean follow-up duration was sometimes less than half of the follow-up period reported. Nine studies concerned only short-term treatment and had follow-ups ranging from 3 days to 3 months duration. In the remaining studies the minimum duration of follow-up reported was 6 months and the maximum in any study 14 years.

Sample size

The number of patients per treatment group in comparative studies with graft patency as the primary endpoint ranged from 14 to 286 with a median of 61. After withdrawals from the studies and exclusions from analysis, these numbers were usually somewhat smaller. The median group size in studies of prosthetic grafts was 34 patients, in studies of vein grafts 86 patients and for studies in which all graft materials were analysed together, 70 patients. Discrepancies between the number of patients studied and the number of grafts studied made it clear that it is common practice to include patients receiving more than one graft twice in a study, either randomising once and counting the two grafts independently or sometimes randomising the same patient a second time once the first observation period was over.

Statistical methods

Analysis of an intention-to-treat (ITT) population was reported as having been performed in only ten studies. Reasons for exclusions from analysis given in 11 studies were varied. Typical of randomised drug trials in general were withdrawal of consent, use of disallowed medication and other medical interventions. Particular to trials involving surgical procedures were patients receiving the wrong operation or no operation, additional secondary procedures and immediate graft occlusion. In the majority of studies (55%) no mention was made of exclusions from analysis.

Statistical comparison of graft patency in the different treatment groups was either by chi-squared test on categorical data at individual time-points (16 studies), log-rank product estimates based on life-table analysis of patency over time (12 studies), Fisher's exact test (two studies) or analysis of time to graft occlusion (ie. duration of patency) by Mann-Whitney U-test in one study. Some studies used more than one method, five studies did not report any statistical methods and two papers made no statistical comparisons. The varied follow-up durations within studies resulted in sample sizes at the end of the follow-up period often being smaller than at the beginning.

Changes in trial design over time

The trial presented and discussed in this thesis was commenced in 1990. However, ten of the studies included in this review were reported after commencement of this trial. As mentioned previously, there was no increase in the use of a double blind design over time, only three of the ten studies reported after 1990 used such a design and only two used a placebo control. However, the use of a multicentre design did appear to increase with five of the eight truly multicentre studies (>2 centres) being reported after 1990. The sample size was correspondingly larger in the later studies: a median of 104 patients per treatment group in the later studies compared to 50 patients prior to 1990.

Review of treatments

Aspirin

The most studied agent for the maintenance of vascular patency in peripheral bypass grafts is aspirin. Sixteen publications were identified in which the results of fourteen studies of aspirin alone or aspirin in combination with dipyridamole were reported (Table 9). Seven of these studies included a placebo control group, three included a comparison with an anticoagulant-treated group and four with an untreated control group. Treatment allocation was randomised in all studies. The placebo-controlled studies will be considered in greatest depth.

Four placebo-controlled studies with a mean treatment group size of 95 patients showed a statistically significant benefit of aspirin on graft failure and three with a mean treatment group size of 152 patients showed no significant difference. Only one of these latter studies found more graft failures in the aspirin group and this difference was not statistically significant. One feature which distinguishes all of the positive studies from the negative studies with aspirin is the duration of follow-up. Those studies with positive results all contained the follow-up data only up to 12 months after surgery. Two of the three negative studies analysed data from two to three years follow-up. The daily dose of aspirin, which varied from 300mg to 1.5g did not seem to influence the results, and time of starting treatment, pre-operatively in five studies and post-operatively in two studies also did not seem to be important. The use of dipyridamole together with aspirin had no consistent effect.

Table 9. Comparative studies of aspirin (ASA) and aspirin + dipyridamole (ASA + DP)

Study	No. of patients (ASA/total)	Design	Follow-up	Endpoints	p-value
Zekert (1975)	ASA 119/247	DB, R, PC, S	14 days	graft patency	n.s.
Ehresmann (1977) Boehme (1977)	ASA 215/428	DB, R, PC, M(2)	≤12 months	graft patency	p<0.003
Harjola (1981)	ASA+DP 93/364 ASA 92/364	O, R, C, S	mean 10 days	graft patency	p<0.001 ASA+DP n.s. ASA
Green (1982)	ASA+DP 16/49 ASA 16/49	DB, R, PC, S	12 months	graft patency	p=0.05
Goldman (1983) and (1984)	ASA/DP 22/53	DB, R, PC, S	12 months	graft patency	p<0.05
Kohler (1984)	ASA+DP 50/100	DB, R, PC, M(2)	2 years	graft patency	n.s.
Donaldson (1985)	ASA+DP 33/65	DB, R, PC, S	12 months	graft patency	p<0.05
Satiani (1985)	ASA 45/100	O, R, C, S	12 months	graft patency	n.s.
Clyne (1987)	ASA+DP 78/148	O, R, C, S	12 months	graft patency limb salvage survival	p=0.012 n.s. n.s.
Kretschmer (1990)	ASA 148/298	O, R, C, S	≤15 years	graft patency survival	n.s. n.s.
McCollum (1991)	ASA+DP 286/549	DB, R, PC, M(48)	≤3 years	graft patency CV events	n.s. p=0.004
Waibel (1976)	16/28	O, R, AC, S vs coumarin	6 months	graft patency	n.s.
Schneider (1979)	30/90	O, R, AC, S vs coumarin	2 years	graft patency	p<0.05 against ASA
Edmondson (1994)	106/200	SB, R, AC, M(8) vs LMWH	12 months	graft patency	p=0.02 against ASA

Design: DB = double-blind, SB = single-blind, O = open,
C = controlled (not placebo), PC = placebo controlled, U = uncontrolled, AC = active control
S = single centre, M (2) = multicentre (2 centres)
R = Randomised parallel group, H = historical controls

Three placebo-controlled studies included only patients with prosthetic grafts. All showed a benefit of aspirin despite treatment group sizes of only 16 to 33 patients (Donaldson *et al* 1985, Goldman *et al* 1983, Green *et al* 1982). In contrast, the only study to include exclusively patients receiving vein grafts, although relatively large, failed to find a significant effect of treatment (McCollum *et al* 1991). Both absolute and relative reductions in occlusion rates were considerably greater in studies with prosthetic bypasses (Table 10). This suggests that the benefit of the drug may be greater in

preventing occlusion of prosthetic grafts, a conclusion supported by an open controlled study which found that overall significant differences were largely due to an effect in the prosthetic grafts included (Clyne *et al* 1987).

Table 10. Change in incidence of occlusions according to bypass material in controlled studies of aspirin (means weighted according to sample size)

Bypass material included in studies	Number of comparisons included	Occlusion rate in control group (%)	Absolute change from control (%)	Relative change from control (%)
Prosthetic only	4	64	-39	-71
Any material	7	22	-9	-39
Vein only	1	33	-3	-9
All studies	12	37	-10	-32

The lack of significant benefit in studies with longer follow-up could reflect a real loss of benefit over time, perhaps due to disease progression, or poorer compliance with the treatment regimen in a longer study, or it may be a consequence of the life-table analysis of patients with different follow-up durations. Another factor was highlighted by Franks *et al* (1992) who showed that compliance with aspirin therapy was poor enough in one large study (McCollum *et al* 1991) to influence the statistical conclusions. In this case it could be concluded that the trial results accurately reflect the value of prescribing aspirin to a population, but do not reflect the value of the drug to an individual patient who diligently takes the treatment.

The results of the controlled studies with aspirin stand up to scrutiny of the trial methods in most respects. All were randomised and most were double-blind. Follow-up was in most cases for at least 12 months. There was a tendency for smaller studies and those with the shorter follow-up to be more positive for aspirin, but this may have been related to the predominance of prosthetic grafts in the smaller and shorter studies. The failure of the largest placebo-controlled study to show a significant difference may have been related to the factors already mentioned, but it is also notable that this was the only truly multicentre study amongst the placebo-controlled studies. The studies included mostly or sometimes exclusively femoropopliteal grafts and only one study (Green *et al*

1982) reported results for below-knee grafts separately. These data were favourable, but not statistically significant.

Cardiovascular mortality was significantly lower with aspirin treatment in one placebo-controlled study (McCollum *et al* 1991), but overall mortality was not. Amongst the other double-blind studies, the number of deaths was too small due to shorter follow-up or a smaller sample size to reach any firm conclusions on an effect on survival.

In spite of the generally larger size of the negative studies, a meta-analysis including mostly the same placebo-controlled studies has shown that in general there is a significant benefit of aspirin on graft patency in peripheral arterial reconstructions (Antiplatelet Trialists' Collaboration 1994a), although this meta-analysis also included a small number of patients undergoing thrombo-endarterectomy. Comparisons of aspirin with anticoagulant therapy after peripheral bypass surgery have been made in three studies, two of which found greater benefit with anticoagulants. All of these studies were randomised, but none of them was double blind.

Ticlopidine

Two controlled trials of the platelet inhibitor, ticlopidine, in peripheral bypass grafts have been reported (Table 11). The open, controlled trial (Shionoya *et al* 1990) showed treatment benefit only in a subgroup of patients with hyperlipidaemia and not overall or in a number of other subgroups analysed. The second trial published had a multicentre, double-blind, placebo-controlled design and showed a significant treatment benefit up to two years in terms of graft patency whether analysed by life-table techniques or by intention-to-treat analysis of patients alive with primary or secondary graft patency (Becquemin 1997). In the ITT analysis the primary patency was 66% with ticlopidine compared to 51% in the placebo group. This study concerned only patients with saphenous vein grafts (39% of which were femorotibial grafts) and included objective confirmation of graft patency, providing strong evidence of the efficacy of ticlopidine in the maintenance of vein graft patency. No data in prosthetic grafts or on comparisons with other agents are currently available.

Table 11. Comparative studies of ticlopidine

Study	No. of patients (active/total)	Design	Follow-up	Endpoints	p-value
Shionoya (1989) + Shionoya (1990)	112/220	O, R, C, M(8)	2 years	graft patency	n.s.
Becquemin (1997)	122/243	DB, R, PC,M(25)	2 years	graft patency mortality major isch. Events	p=0.02 n.s. n.s.

Design: DB = double-blind, SB = single-blind, O = open,
C = controlled (not placebo), PC = placebo controlled, U = uncontrolled, AC = active control
S = single centre, M (2) = multicentre (2 centres)
R = Randomised parallel group, H = historical controls

Other platelet inhibitors

Studies of platelet inhibitors other than aspirin and ticlopidine in this indication included two controlled studies of sulphinpyrazone, and one of indobufen (Table 12). Dipyridamole was included as an addition to aspirin in ten studies (included in a previous section) and also tested alone against aspirin and control groups in one study with a short follow-up (Harjola 1981). This open study of a variety of arterial reconstructive procedures showed a small, but not statistically significant reduction in graft occlusions with dipyridamole compared to an untreated control group (6% dipyridamole v 14% control).

The two studies of sulphinpyrazone were both placebo-controlled, double-blind and randomised. They included 232 patients in total and both reported follow-up of over 85% of the patients entered. There was no reduction in graft occlusion in either study. The larger of the two studies included aortoiliac as well as femoropopliteal procedures, but 137 out of 164 cases followed up were femoropopliteal procedures. Both vein and prosthetic bypasses were included and stratification was employed at the time of randomisation. The other study included only 6% prosthetic grafts and reported a very low failure rate (15%) even in the placebo group. Despite the performance of controlled trials with sulphinpyrazone and dipyridamole, there is currently no firm evidence to support their use in this indication. The size of the trials, the small number of prosthetic grafts included and the number of graft occlusions reported could, however, have resulted in a worthwhile clinical benefit being missed.

Another platelet inhibitor working by cyclo-oygenase inhibition, indobufen, was compared in one study with aspirin in a double-blind multicentre study of 12 months

therapy in 113 patients with PTFE grafts. Indobufen was not shown to offer any advantage over aspirin (patency 60% indobufen v 52% aspirin) and there are no reports of placebo-controlled studies with this agent.

Table 12. Comparative studies of platelet inhibitors other than aspirin

Study	No. of patients (active/total)	Design	Follow-up	Endpoints	p-value
Dipyridamole Harjola (1981)	93/364	O, R, C, S	mean 10 days	graft patency	n.s.
Sulphinpyrazone Blakely (1977)	75/164	DB, R, PC	3 years	graft patency periph vasc events	n.s. n.s.
Sulphinpyrazone Comberg (1983)	27/54	DB, R, PC, S	6 months	graft patency	n.s.
Indobufen d'Addato (1992)	56/113	DB, R, AC, M(9)	12 months	graft patency	n.s.

Design: DB = double-blind, SB = single-blind, O = open,
C = controlled (not placebo), PC = placebo controlled, U = uncontrolled, AC = active control
S = single centre, M (2) = multicentre (2 centres)
R = Randomised parallel group, H = historical controls

Oral anticoagulants

Studies have been reported with various coumarin derivatives as long-term prophylactic anti-thrombotic treatment. These are summarised in Table 13. A total of five different studies of patients receiving coumarins after peripheral bypass surgery appear to have been performed. In two studies successive reports have been published with either extended follow-up or increased numbers of patients. This was possible because none of the studies was double-blind and placebo-controlled.

Of the five studies, one included a total of only 28 patients in a comparison with aspirin, too few patients to demonstrate whether the effect observed was likely to be genuine. Another study with 30 patients / treatment group did show a superior effect to aspirin on graft patency after 2 years ($p<0.05$) in patients receiving femoropopliteal vein grafts. The two largest studies had similar sample sizes and both had untreated control groups, but reported contradictory results after 5 year follow-ups. A Swedish study failed to find any significant differences in graft patency (46% coumarin v 42% control), limb salvage or patient survival (Arfvidsson *et al* 1990). A variety of reconstructions were

studied including both vein and prosthetic bypasses. In contrast, Kretschmer *et al* (1988) reported a significant improvement in patient survival with coumarin, but did not appear to have shown a significant effect on graft patency after 5 years (82% coumarin v 71% control). However, earlier and later analyses of what was probably largely the same group of patients with a shorter and longer follow-up did show a significant reduction in graft failure (Kretschmer *et al* 1986 and 1996). Only femoropopliteal vein grafts were included. Anticoagulant treatment in the different studies was instituted at varying times between 1 and 14 days post-operatively.

The last and most recent study demonstrated a significant benefit of long-term warfarin when added to aspirin in the treatment of high risk vein grafts, those with poor run-off poor quality vein or re-do procedures (74% warfarin v 51% control). The benefit was evident in both graft patency and limb salvage despite a small sample size of 64 grafts in 56 patients (Sarac *et al* 1998).

Blinding investigators in studies with oral anticoagulants is clearly difficult due to the need to monitor the anticoagulant effect. However, one double-blind study has been reported in patients with arterial disease, in which the anticoagulant treatment was monitored at a different centre from that monitoring the clinical outcome (de Smit *et al* 1987). Unfortunately, this study did not include patients with infra-inguinal bypasses. Without such studies of graft patency and in view of the rather mixed results published so far, the case for using oral anticoagulants routinely for the maintenance of peripheral bypass patency does not seem to have been proven. The evidence in their favour to date has been obtained only in vein grafts.

Low molecular weight heparin

Two comparative trials of subcutaneously administered low molecular weight heparins (LMWH) have been reported in this indication. These were open randomised comparisons of dalteparin sodium with aspirin plus dipyridamole in 200 patients undergoing femoropopliteal bypass (Edmondson *et al* 1994) and of enoxaparin with unfractionated heparin (UFH) in 201 patients with below-knee grafts (Samama *et al* 1995). In the former study most patients received prosthetic grafts (73.5%) and had an above-knee distal anastomosis (69%). There was an absolute difference in primary patency of 15.4% in favour of LMWH at 12 months (aspirin rate 72%). This was significant on a log-rank test, but further investigation of the different indications for surgery showed that the difference was large in patients with severe ischaemic symptoms

(36%) and very small in those with only claudication (5%). The difference in indications was independent of other factors which might have influenced outcome.

Table 13. Comparative studies with oral anticoagulants and low molecular weight heparins (LMWH)

Studies	No. of patients (active/ total)	Design	Follow-up	Endpoints	p-value
Waibel (1976)	16/28	O, R, AC, S	6 months	graft patency	n.s.
and (1981)			5 years	graft patency	n.s.
Schneider (1979)	30/90	O, R, AC, S	2 years	graft patency	p<0.05
Kretschmer (1986)	34/71	O, R, C, S	18 months	graft patency	p<0.04
and (1987)	42/88		30 months	graft patency	p<0.03
and (1988)	60/119		5 years	graft patency	n.s.
				survival	p=0.043
and (1992)	66/130		10 years	graft patency	p<0.006
				limb salvage	p<0.012
				survival	p=0.055
and (1996)	66/130		14 years	graft patency	p<0.012
				limb salvage	p<0.012
				survival	p<0.029
Arfvidsson (1990)	61/116	O, R, C, S	5 years	graft patency	n.s
				limb salvage	n.s
				survival	n.s.
Sarac (1998)	37/64	O, R, C, M(2)	3 years	primary patency	p=0.04
				limb salvage	p=0.02
LMWH Edmondson (1994)	94/200	SB, R, AC, M(8)	12 months	Primary patency	p=0.02
Samama (1995)	101/201	O, R, AC, M(14)	30 days	graft patency	p=0.025
McMillan (1997)	28/69	O, H, AC, S	30 days	graft patency	n.s.

Design: DB = double-blind, SB = single-blind, O = open,
C = controlled (not placebo), PC = placebo controlled, U = uncontrolled, AC = active control
S = single centre, M (2) = multicentre (2 centres)
R = Randomised parallel group, H = historical controls

The latter study looking at enoxaparin, consisting mostly of vein grafts (68%) with a majority below-knee (90%), followed the patients for only 30 days, but showed a significant absolute reduction of 13% in the number of occlusions (patency in LMWH 89% v UFH 76%). Another smaller study with enoxaparin which used historical controls and

also followed the patients for only 30 days did not show any difference in graft occlusions, but reported a very low 4% overall failure rate despite including mostly prosthetic below-knee grafts (McMillan *et al* 1997). No double-blind trial with a LMWH has been reported.

Dextrans

Dextrans have been investigated as an intravenous infusion given intra-operatively and for three days after surgery (Table 14). Graft patency at 3 days (Waibel 1976) and one week (Rutherford *et al* 1984) after surgery has been shown to be improved by dextran 40 in comparison with an untreated control group or in addition to standard intra-operative treatment with heparin. The second of these two studies was a randomised, multicentre trial, but neither study was conducted in a double-blind fashion. The benefits found by Rutherford *et al* (1984) were evident only in grafts to the tibial or peroneal vessels and were not seen in autogenous vein grafts. Over two hundred patients were randomised into this study, but 26% were excluded from the efficacy analysis. Only a one month follow-up was reported initially (patency 85% dextran v 79% control) and a later publication on the patient population of the trial confirmed that no long-term effect on patency was observed (Rutherford *et al* 1988). A more recent single centre study in reversed vein grafts confirmed in an ITT analysis that there was no benefit at 30 days in graft patency or in the number of patients alive with a patent bypass (90% dextran v 91% control) (Katz *et al* 1998). Two further studies have been published on this use of dextran 40: an uncontrolled series of 26 patients with femoropopliteal bypasses (Foster *et al* 1966) and a study of dextran 40 alone compared to the combination with warfarin (Kluge *et al* 1972) which suggested that the combination gave better results. This last paper reported carefully defined clinical endpoints instead of graft patency, but no mention was made of randomisation or blinding.

Two controlled studies suggest an effect of dextran 40 on short-term patency of high risk grafts (up to 1 week post-operation), but the largest study was negative in a more general population. Studies with a placebo control and a controlled longer follow-up are lacking, preventing any firm conclusion from being drawn.

Table 14. Comparative studies of dextran 40

Study	No. of patients (dextran/total)	Design	Follow-up	Endpoints	p-value
Waibel (1976)	64/131	O, R, C	3 days	graft patency	p<0.05
Rutherford (1984)	73/156	O, R, C, M(9)	1 week 1 month	graft patency graft patency	p<0.05 n.s.
Kluge (1972)	?/43	O, AC, S	58 months	clinical improvement	p<0.01
Katz (1998)	126/273	O, R, C, S	30 days	graft patency	n.s.

Design: DB = double-blind, SB = single-blind, O = open,
C = controlled (not placebo), PC = placebo controlled, U = uncontrolled, AC = active control
S = single centre, M (2) = multicentre (2 centres)
R = Randomised parallel group, H = historical controls

Prostaglandin E_1

In three publications on two studies, prostaglandin E_1 (PGE_1) was administered for 2-10 days either intra-arterially or intravenously (Table 15). Both studies included only patients with below-knee grafts, but with distal anastomoses on both the popliteal and crural arteries. Significant benefit of PGE_1 on graft patency or limb salvage was reported in both papers in either the distal bypasses or the whole study group. However, neither trial was double-blind and only one trial was randomised with a parallel control group (Fietze-Fischer *et al* 1987). The other study employed historical controls (Tanabe *et al* 1984). Short-term benefits were shown in the open parallel-group controlled study with 10% reduction in failure at 3 days and a reduction in forefoot and borderline amputations at discharge. Primary patency at discharge was 90% with PGE_1 and 80% in the control group. However, no follow-up after discharge from hospital was reported in these patients. A long-term follow-up in a double-blind, placebo-controlled study is still required in order to demonstrate any prolonged clinical benefit of early post-operative parenteral therapy with PGE_1.

Table 15. Comparative studies of prostaglandin E_1

Study	No. of patients (PGE_1/total)	Design	Follow-up	Endpoints	p-value
Fietze-Fischer (1987)	50/99	O, R, C, S	3 day	graft patency	p=0.056
Gruss (1988)			Discharge	graft patency	n.s.
				amputation	p=0.031
Tanabe (1984)	28/113 fem-pop	O, C, H, M(5)	>3 months	graft patency	p<0.01
	14/52 fem-tib		>3 months	graft patency	p<0.05

Design: DB = double-blind, SB = single-blind, O = open,
C = controlled (not placebo), PC = placebo controlled, U = uncontrolled, AC = active control
S = single centre, M (2) = multicentre (2 centres)
R = Randomised parallel group, H = historical controls

Meta-analysis of platelet inhibitor trials

A meta-anlysis was performed, as described, of all randomised trials of platelet inhibitor drugs acting on the cyclo-oxygenase enzyme, aspirin and sulphinpyrazone. This was essentially a repeat of a published meta-analysis (Antiplatelet Trialists' Collaboration 1994a) with the addition of two additional trials and, importantly, an investigation of the sources of the heterogeneity noted amongst the results of these trials.

Eleven trials were identified which satisfied the criteria for inclusion, being randomised, prospectively planned and with a concurrent control group not receiving any antithrombotic treatment. These trials are listed with the principal data which were included in the analysis (Table 16). The trials were published in the period between 1975 and 1991. There was no evidence of an association of outcome with the date of publication, i.e. more recent trials were not consistently more, or less, positive than earlier trials.

Table 16. Trials and data analysed by order of publication

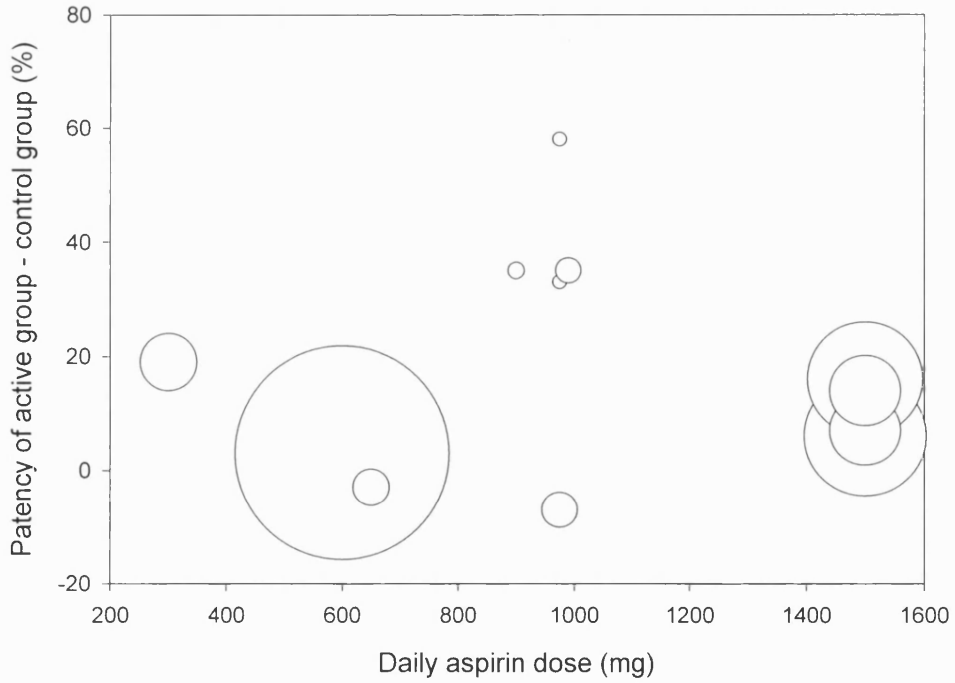
Trial	Drug*	Active: occluded / total	Control: occluded /total	% patent (drug - control)	s.e. of the difference (%)	No. of centres	Follow-up (month)	Prosthetic grafts (%)	PAOD stage III/IV (%)	Below-knee graft (%)	Current smoker (%)
Zekert 1975	A	19 / 148	28 / 150	6	4	1	<1	-	53	-	-
Ehresmann 1977	A	24 / 139	47 / 141	16	5	2	12	29	26	-	91
Harjola 1981	A A + DP	6 / 92 0 / 93	12 / 86	7 14	5 4	1	<1	-	-	-	-
Green 1982	A A + DP	2 / 16 6 / 16	12 / 17	58 33	14 16	1	12	100	84	47	55
Comberg 1983	S	4 / 27	4 / 27	0	10	1	6	6	31	-	-
Goldman 1983	A + DP	7 / 21	19 / 28	35	14	1	12	100	79	45	81
Kohler 1984	A + DP	15 / 44	12 / 44	-7	10	2	24	30	67	62	-
Donaldson 1985	A + DP	4 / 33	15 / 32	35	10	1	12	100	0	34	-
Satiani 1985	A	8 / 45	8 / 55	-3	7	1	12	37	88	68	63
Clyne 1987	A + DP	12 / 72	25 / 70	19	7	1	12	37	59	80	61
McCollum 1991	A + DP	86 / 286	86 / 263	3	4	48	30	0	60	59	41

* A=aspirin, DP=dipyridamole, S=sulphinpyrazone

Five trials compared aspirin alone with a control group and seven trials compared aspirin plus dipyridamole with a control group. Two of the trials included both aspirin alone and aspirin plus dipyridamole and presented comparisons of each with a common control group. One trial was a comparison of sulphinpyrazone with placebo. Nine of the trials identified were double-blind, placebo controlled trials previously included in the meta-analysis and two were open comparisons with an untreated control group which had not been included in the published meta-analysis.

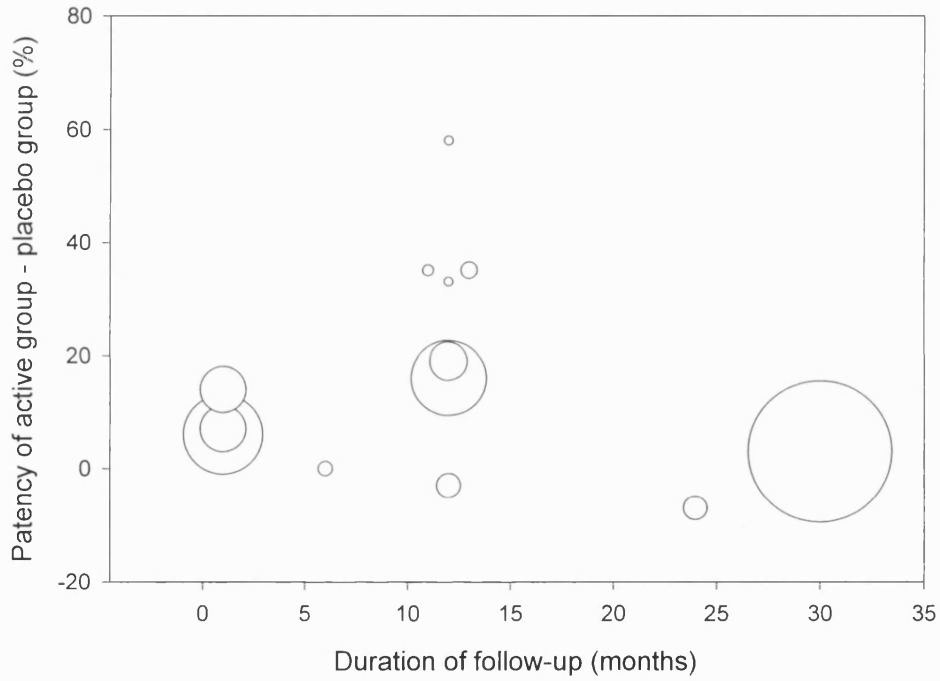
Overall the mean results from the comparisons with aspirin alone indicated 17% (±24) higher patency with active treatment while the results from comparisons with aspirin plus dipyridamole showed 19% (±17) higher patency with active treatment. The dose of aspirin used ranged from 300 mg/day to 1500 mg/day. There was no clear relationship between the dose of aspirin used in the trial and the result of the trial (Figure 3). The difference in outcome between the two treatment groups was 8% (±16) in the open trials and a mean of 18% (±20) from the double-blind trials, both in favour of the active treatment.

Figure 3. Relationship between daily aspirin dose and the difference in patency rates.
Bubble diameter is proportional to the sample size



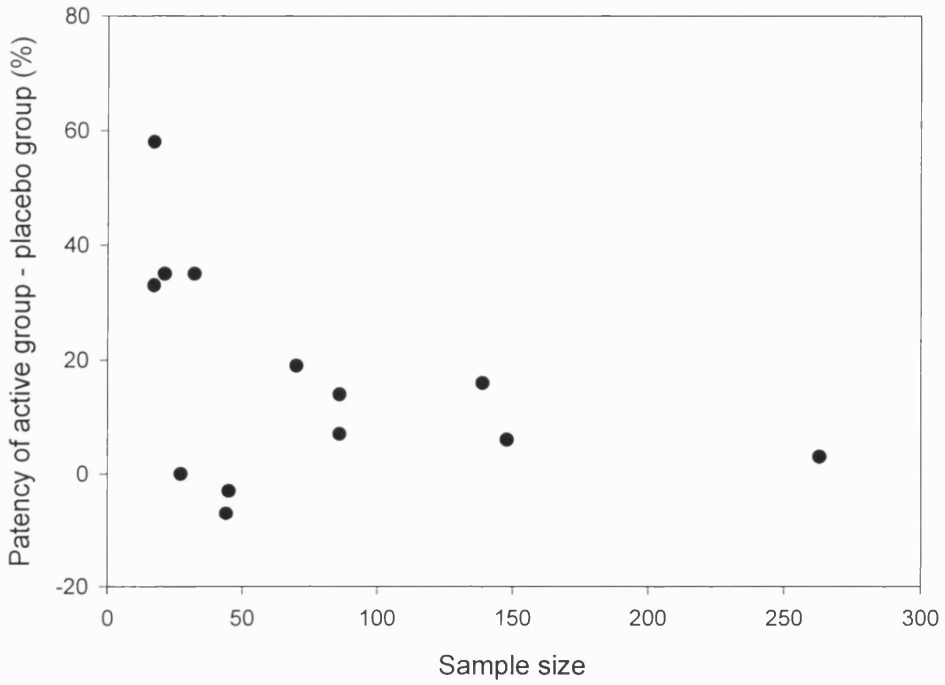
The duration of treatment and follow-up ranged from 10 days in one trial to thirty months in another. Trials with very short follow-up of less than one month had rather small differences between the treatment groups, as did the two with the longest duration of treatment period. Those trials with a follow-up duration of 12 months, however, had generally good results for anti-platelet therapy resulting in no consistent trend over time (Figure 4).

Figure 4. Association of duration of follow-up with the difference in patency between the groups. Bubble diameter is proportional to sample size.



The difference in patency rates was greatest amongst those trials with the small sample size (Figure 5). There was a weak inverse association of difference in patency with sample size, r=-0.55. This did not appear to be related to the number of centres recruiting patients. Single centre trials, which comprised the majority of the trials, provided both the best and worst results for the active treatment.

Figure 5. Association of sample size with difference in patency rates between the groups



Information on the proportion of patients receiving prosthetic bypass grafts was available from nine trials which included ten different active groups. There was a strong association between outcome and the proportion of prosthetic bypasses included, with a larger proportion of prosthetic grafts being associated with a more favourable outcome for anti-platelet treatment. This is shown as a bubble plot to illustrate the sample size (Figure 6) and as a scatter plot with standard errors of the differences between the patency rates to show the precision of the estimate (Figure 7). The proportion of prosthetic bypasses was also inversely associated with sample size in the trial, r=-0.74 (Figure 8).

Figure 6. Association of the percentage of patients with prosthetic grafts with the difference in patency between the groups. Bubble size is proportional to sample size.

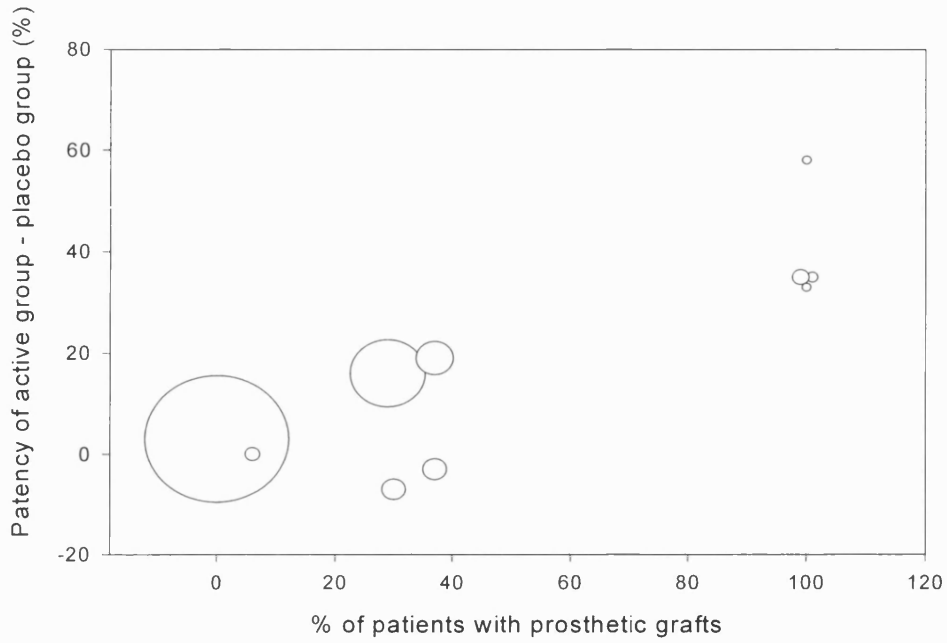


Figure 7. Association of the percentage of patients with prosthetic grafts with the difference in patency between the groups. Differences are plotted with standard errors.

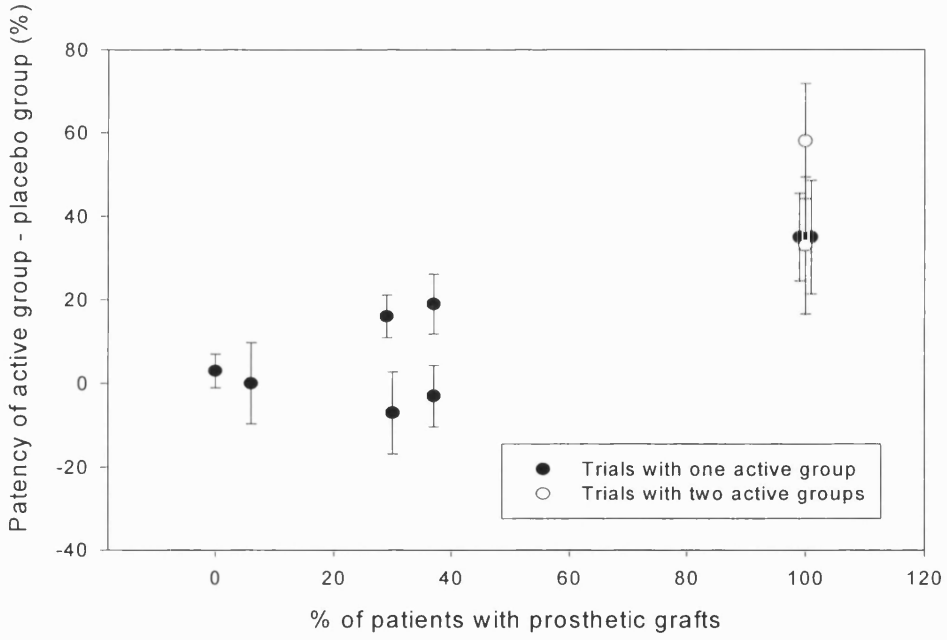
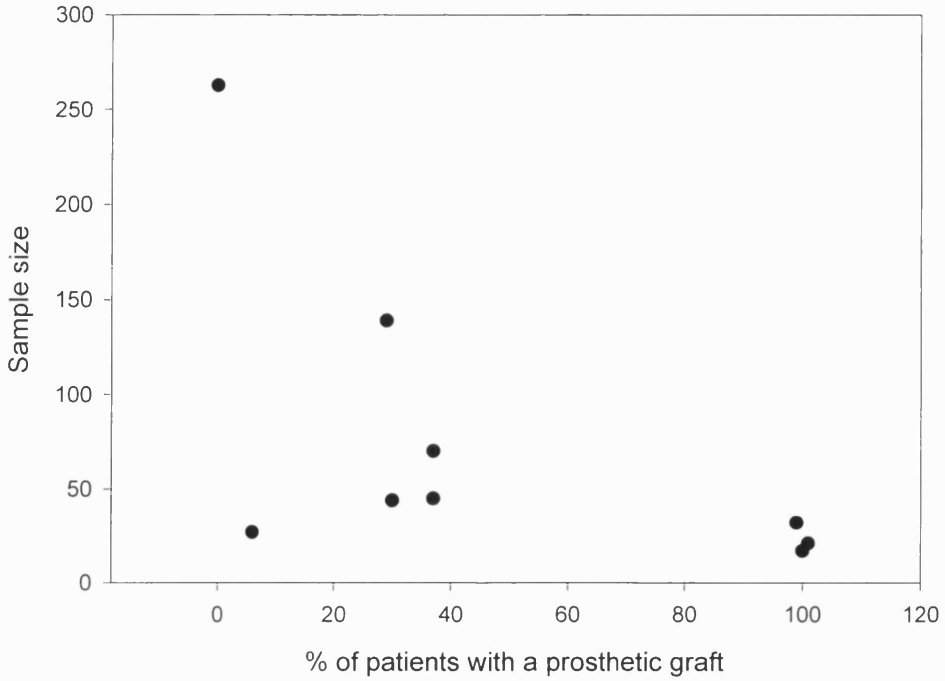


Figure 8. Association of the percentage of patients having prosthetic grafts with the sample size.



The level of bypass was described in nine trials. The majority of trials included only infra-inguinal bypass procedures. There was weak evidence of an association of the proportion of above-knee grafts with the result of the trial, more above-knee grafts corresponding to a greater benefit of platelet inhibition (Figure 9). However, the proportion of above-knee grafts also appeared to be associated with the proportion of prosthetic grafts used in a trial (Figure 10).

Figure 9. Association between the percentage of patients with above-knee grafts and the difference in patency rates. Bubble diameter is proportional to sample size.

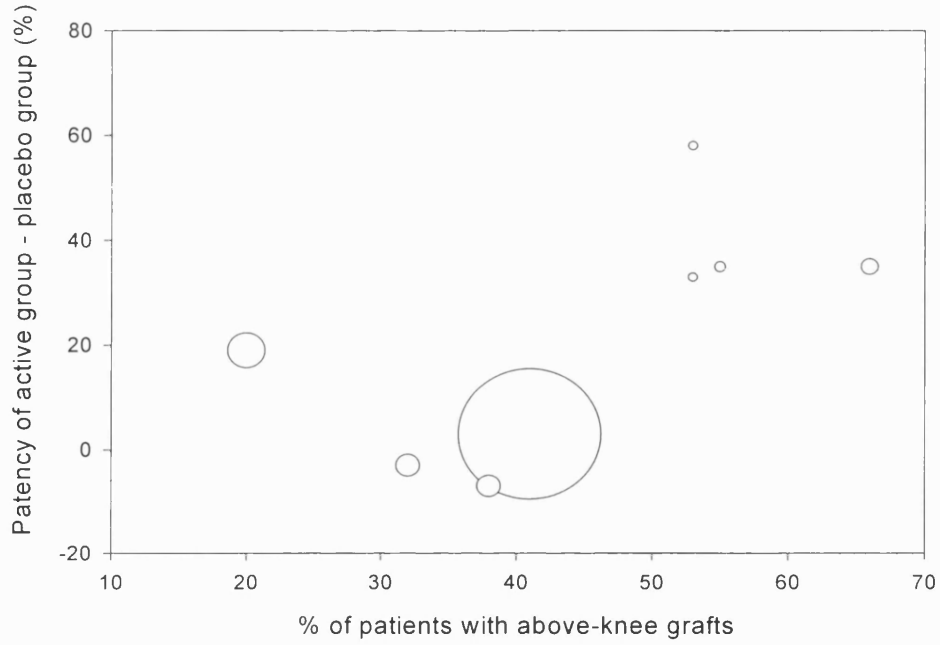
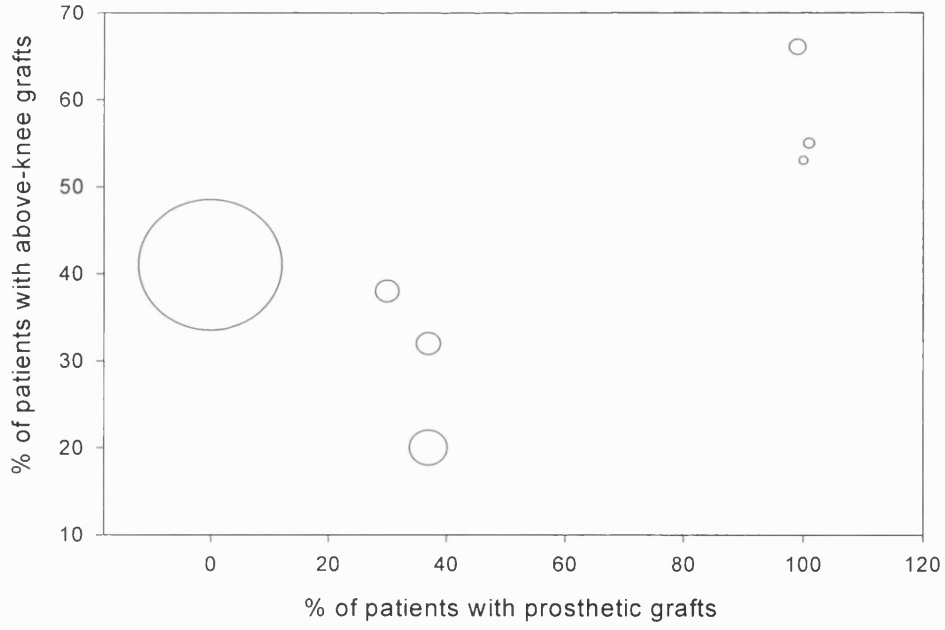


Figure 10. Association of the percentage of patients with prosthetic bypasses with the percentage of patients with above-knee grafts. Bubble diameter is proportional to sample size.



The severity of ischaemic symptoms was described in ten trials. In all but one trial a mixture of patients with intermittent claudication and those with ischaemic rest pain or trophic lesions were included, but the proportion of patients in the trial with severe ischaemic symptoms did not appear to be associated with the efficacy of platelet inhibitors. Only seven of the trials reported the number of current smokers included and no clear relationship was discernible between the proportion of such patients in the trial and the efficacy of aspirin.

Multiple logistic regression analysis confirmed the overall benefit of platelet inhibitor treatment, but also confirmed that the trial results were heterogeneous. Inclusion in the analysis of information on the proportion of patients in each trial receiving prosthetic bypass grafts indicated that this was a significant source of the heterogeneity in the outcomes. The analysis indicated that the sample size of the trials was a less significant contributor to the heterogeneity observed and neither the treatment regimen used nor the level of bypass contributed significantly to the differences between the trials in this analysis.

The logistic regression analysis was repeated with subsets of the trials in order to test the robustness of the conclusions. Exclusion of the open and single-blind trials not previously included in the published meta-analysis and exclusion of the single trial using sulphinpyrazone each failed to alter the conclusion that the proportion of prosthetic grafts in a trial was a significant source of the heterogeneity of the trial results. The effectiveness of platelet inhibitors in reducing peripheral bypass occlusion was strongly associated with the proportion of patients having prosthetic bypass grafts.

Discussion of meta-analysis results

A conclusion of the previously published meta-analysis of platelet inhibitor trials in the maintenance of vascular patency was that such therapy was effective in reducing the number of occlusions in vascular reconstructions (Antiplatelet Trialists' Collaboration 1994). However, previous work has shown that graft occlusion is influenced by a number of factors (Bergamini *et al* 1991, Sayers *et al* 1994) and the principal mechanisms of graft failure are considered to differ according to the graft material (Bergqvist 1985).

Subgroup analysis of patients with vein and prosthetic bypass grafts in one of the trials included in this review indicated the possibility that aspirin might be principally of benefit in patients receiving prosthetic grafts (Clyne *et al* 1987). Those findings are supported by this review, which suggests that the evidence for a benefit of platelet inhibition in the maintenance of vein graft patency is weak.

The evidence in this analysis for the prosthetic grafts being the source of positive results with aspirin in these trials is complicated by two possible confounding factors. The sample size of the treatment groups and the type of bypass procedure performed, above-knee or below-knee, were also associated with both the outcome and the use of prosthetic graft material. It is possible that sample size was the important factor and that there is a more pronounced publication bias in small, single centre trials leading to non-publication of small negative trials. However, the evidence of subgroup analyses from various trials suggests that the positive results were likely to have been due to the use of prosthetic grafts. The smaller size of the trials including only patients with prosthetic grafts is probably due to the smaller number of such procedures performed in most centres when compared to the number of vein graft procedures. The association of the proportion of prosthetic grafts used with the level of the bypass procedure is to be expected, since prosthetic materials are rarely used in below-knee procedures due to the generally better results obtained in long bypasses to the smaller arteries with autogenous saphenous vein (European Working Group on Critical Limb Ischaemia 1991). A poorer outcome from anti-platelet therapy in more distal grafts could result from a greater role of poor run-off in the failure of these procedures, which would not be expected to be affected by antiplatelet therapy. Previous investigations of a relationship between the level of bypass and the efficacy of anti-platelet therapy have, however, failed to show any difference in results between above and below-knee procedures (Kohler *et al* 1994, Ehresmann *et al* 1977).

It has been postulated that the outcome of the largest trial exclusively in vein grafts (McCollum *et al* 1991) was confounded by poor compliance in the aspirin group and uncontrolled use of aspirin in the control group (Franks *et al* 1992). This could also have been true of other trials. However, in this context it should be noted that over the period in which these trials took place there was no consistent trend for a reduction in difference between aspirin and placebo, although the prescription of aspirin as an anti-thrombotic agent has probably increased in this period.

The aspirin trials in this review are the same as those previously included in a meta-analysis with the addition of one single-blind trial (Satiani 1985) and one open, controlled trial (Clyne *et al* 1987). The likelihood of bias in open or single-blind trials would usually dictate that only double-blind, placebo-controlled trials should be included in such an analysis. However, both the trials included were otherwise well designed and the principal outcome variable of bypass patency was objectively verifiable making bias less likely. Exclusion of these trials did not change the conclusions of the present analysis. The previous meta-analysis also included three trials of other platelet inhibitory drugs.

Two were excluded from this review, because one of them concerned principally patients undergoing thrombo-endarterectomy and the other was published only as an congress abstract with too little information for a satisfactory analysis of the trial methodology. One trial of sulphinpyrazone in peripheral bypass procedures was included in this review. Exclusion of the sulphinpyrazone trial did not alter the statistical conclusions.

The analysis of differences between the results of trials in this area is constrained by the rather small number of randomised controlled trials. However, there are sufficient data to demonstrate that the results of meta-analysis of anti-platelet therapy with cyclo-oxygenase inhibitors such as aspirin for prevention of graft failures should not be applied indiscriminately to all peripheral bypass procedures, since the reduction in bypass graft occlusion obtained was strongly associated with the proportion of prosthetic grafts included in the trial. It is important that clinical trials are designed to investigate separately the efficacy of platelet inhibition in vein and prosthetic bypass grafts. The value of aspirin in the general reduction of cardiovascular morbidity and mortality (Antiplatelet Trialists Collaboration 1994a) is not challenged by this result, however, only its value in preventing vein graft occlusion.

The greater efficacy of aspirin in preventing occlusion of prosthetic grafts may be due to the greater thrombogenicity of prosthetic grafts. In contrast to the trial results with aspirin, a recent trial in femorodistal vein bypass grafts with a different type of inhibitor of platelet aggregation, ticlopidine, has shown a significant effect of the drug in reducing bypass occlusion (Becquemin 1997). Ticlopidine is thought to act by reducing ADP-induced platelet aggregation, whereas the action of aspirin is to inhibit platelet aggregation by the inhibition of thromboxane A_2 production. *In vitro* tests indicate a more greater effect of aspirin on collagen and arachidonic acid induced platelet aggregation than on that induced by ADP. This suggests that different types of antiplatelet agents may be appropriate in different types of grafts.

This analysis also serves to reinforce the argument that plausible sources of heterogeneity should always be investigated when undertaking a meta-analysis. Sometimes this aspect is not fully investigated arguing that there is usually insufficient power to detect heterogeneity through formal statistical testing. However, it has been argued that sensible investigation of sources of heterogeneity involving statistical testing, graphical display and clinical insight should increase the scientific and clinical relevance of the analysis (Thompson *et al* 1994). Ideally, this meta-analysis would have been carried out using patient level data. These were not available and so some further assumptions and approximations were necessary. Nevertheless, the level of heterogeneity present in this situation could still be identified using standard multiple

logistic regression models. Absence of patient level data therefore should not preclude such investigations.

In summary, further analysis of the studies in peripheral bypass grafts does not support the conclusion that antiplatelet agents are effective in all types of bypass grafts. This analysis also exemplifies the importance of examining potential sources of heterogeneity as part of a meta-analysis and shows that this can be a useful source of information on the value of pharmacotherapy in the maintenance of peripheral bypass grafts.

General discussion of the literature review

Certain design characteristics are clearly desirable in clinical trials of adjuvant therapy in bypass surgery. The presence of a placebo control group and the use of a double-blind randomised design are general requirements for proof of efficacy of a new treatment which are applicable in this indication. Well-defined patient groups, adequate sample size, relevant endpoints and intention-to-treat analysis are also important. As an alternative to a placebo control, a recognised active treatment could be used as a comparator. Aspirin would seem to be the most acceptable here, particularly in prosthetic grafts.

It might seem that the use of blinding in assessment of outcomes is unnecessary when the main study endpoint is graft patency, since this can be objectively determined and verified. However, an important benefit of blinding the clinicians performing a study is to ensure the impartial allocation of patients to treatment group. With the presence of other factors, such as bypass material and indication for surgery, which can influence outcome, this is essential to be sure that an unbiased result has been obtained. The use of randomisation without blinding is not a guarantee of this since there are always patients who are considered for entry into a clinical trial, but who are ultimately not entered for one reason or another. Knowledge of the treatment to be given could influence this decision.

Half of the trials reviewed here did not have a double-blind design. These were most commonly trials of anticoagulants, dextran 40 and prostaglandin E_1. The lack of blinded studies of these agents seriously undermines the value of the evidence in their favour. In the case of coumarins, the requirement to monitor the prothrombin time regularly throughout the period of treatment makes complete blinding genuinely difficult, but not impossible, as demonstrated by the study of de Smit *et al* (1987). The solution in

that study was to have the patients assessed by observers who were not involved in the administration and monitoring of the study drug. Dextran 40 and prostaglandin E_1 are both administered by intravenous infusion which makes administration of a placebo treatment more difficult practically and ethically, although similar problems have not prevented the conduct of placebo-controlled trials of intravenous prostaglandins in other indications. Double-blind trials have also been performed with LMWH in coronary artery disease despite the need for subcutaneous injections with these agents, demonstrating that this should be possible in peripheral vascular trials (Cohen *et al* 1997). The high proportion of double-blind studies amongst those investigating aspirin use gives a greater degree of confidence in the results with this agent, although the greater use of placebo probably reflects also the greater ease of giving placebos for an oral therapy.

The use of matching placebos help to keep the observer blind as to treatment allocation, but a degree of unblinding can occur with some treatments. Examples of how this can occur inadvertently are the reporting of typical side-effects such as bleeding events in patients on antithrombotic drugs or flushing in patients on some vasoactive medications. Unblinding may also occur if additional investigations on the patient reveal recognisable effects as in the inhibition of platelet aggregation tests by aspirin. Nonetheless, masking the treatment identity is effective in eliminating certain biases from patient allocation to treatment group and will reduce, if not completely remove, the possibility of bias in assessment of outcome.

Despite the greater failure rate of distal bypass grafts compared to more proximal procedures, there have been relatively few studies investigating the use of adjuvant therapy specifically in these difficult procedures. There are probably two reasons for this. Firstly, distal bypasses are a relatively recent development in vascular surgery, and secondly, multicentre trials would usually be required in order to enrol a sufficient number of patients. The results of studies in more proximal procedures may also be relevant to choosing the appropriate pharmacotherapy for distal bypass, but the results of trials with dextran 40, for example, suggest that certain agents may be indicated only in the more difficult distal bypasses. Different procedures should therefore be the subject of separate trials or a separate analysis specified *a priori*. The same is true of the different graft materials. The graft materials included were mixed in about half of the studies despite the commonly held view that the mechanisms of failure may differ in vein and prosthetic grafts (Bergqvist 1985). It could therefore be expected that different treatments might prove to be appropriate for different materials. Evidence for just such a finding was noted in the section on trials of aspirin and confirmed in the meta-analysis. Analysing different

graft materials together may therefore result in exaggeration of the effect in one material or underestimating the effect in another material.

The technical success of the bypass procedure is most clearly demonstrated by determining the patency of the graft. However, the clinical outcome is also important and it was notable that few studies reported the outcome in terms symptoms of ischaemia or the patient's quality of life. This could most easily be assessed by amputation rates, which are particularly appropriate when more distal 'limb salvage' procedures are being studied, and by documenting the patient's symptoms in terms of exercise capacity, rest pain, analgesia consumption and presence of trophic lesions. In the case of an appropriate choice of operation, it might be expected that the clinical outcome would correlate with graft patency, but cases of grafts occluding without regression of symptoms to their previous severity and patients with patent grafts being amputated are well known. The impact of adjuvant therapy on the patient's quality of life should be investigated at least in this simple manner. Patient survival, although more often reported than limb survival, was also missing from half of the reports reviewed and is of great importance in a group of patients who usually have widespread atherosclerotic disease and have a 20% mortality rate within one year (Wolfe 1986, Zdanowski *et al* 1998).

Some of the studies had insufficient power to show any but the most remarkable effects on bypass patency. The average primary patency rate at 12 months in the control groups in the studies reviewed was of the order of 70%. The mean treatment effect shown in the reviewed trials in a controlled study was a 20% absolute improvement in patency. A sample size of at least 72 patients per treatment group would be required to demonstrate such a difference with only 80% power. With 90% power 92 patients per group would be required. A more modest target of an absolute improvement in the patency rate of 15% would probably be the most achievable in vein grafts and would require respectively 91 or 119 patients per treatment group for 80% or 90% power. An improvement of 10% might also be considered clinically worthwhile, but would require more patients still. In fact only seven of the 27 trials included more than 90 patients per group giving reasonable confidence in the result.

A specific requirement of trials in bypass surgery is a follow-up duration of at least 12 months which is required to show a clinically worthwhile result. This is should be of interest even when the treatment is specifically aimed at reducing immediate graft failure. In this case it is important to know if the effect is only temporary or if the whole patency curve is shifted upwards. The trials of dextran 40 and prostaglandin E_1 failed to address the long-term value of the treatment. Results of longer follow-up would also be of

interest, but the 12 month period encompasses the early post-operative period during which the failure rate is greatest and also the time from three to 12 months when grafts are at greatest risk from restenosis.

The fate of all patients in a trial should ideally be determined for the whole follow-up period reported. However, it is common practice in bypass studies to show Kaplan-Meier plots including many patients who have been followed for varying lengths of time with the later fate of many patients quite unknown. It is more time-consuming to follow all patients for a long period, but this reflects the common tendency to analyse and publish results soon after the last patient has been recruited. One consequence of this is that the sample size analysed at the end of the follow-up is often substantially less than the number of patients entered. It has recently been shown that it cannot be assumed that patients whose fate is known are representative of all those entered into a study of distal bypass procedures (Jensen *et al* 1996). Such analysis may seriously underestimate the bypass failure rate. Although life-tables and Kaplan-Meier plots are the most widely used methods of illustrating the graft patency rate in a patient population, the method is not without drawbacks (Underwood *et al* 1984). Life-tables are of assistance in estimating the likelihood of graft patency only in the case that the patient survives up to a given time point without undergoing a major amputation. Patients who are lost to follow-up of graft patency due to death, amputation with a patent graft or other causes are censored, i.e. excluded from the analysis after the interval in which the last patency assessment was available. In other words the number of patients represented in the analysis is ever decreasing, so that the patency rate quoted at the end of follow-up is not the actual percentage of the original population who had a patent graft at the end of the planned observation period. There is probably no perfect solution to this problem, but it might be of additional value to report the percentage of patients entered who are known to be alive with a viable limb and a patent graft at the end of follow-up. This would permit the performance of an analysis on an intention-to-treat population without the appreciable numbers of missing patients common to the life-table method.

The majority of trials were single centre, and only three truly multicentre, double-blind, randomised trials have been published. Only one of these showed a difference between the treatment groups. This may reflect a real difficulty in performing multicentre trials in surgical procedures. Technical factors can vary and are strong determinants of outcome. Policy on patient selection for surgery may also vary between centres. The combination of these factors increases the difficulty in agreeing protocols for multicentre trials and may act as a disincentive to participation. However, the influence of these

centre differences on outcome also makes it difficult to assess the relevance of the results of single centre trials to the general use of adjuvant therapy.

The importance of trial design in the assessment of adjuvant therapy for peripheral bypass procedures should not be underestimated. It may not be coincidental that 73% (11/15) of the open or single-blind trials reviewed showed a significant effect of treatment on graft patency compared to only 43% (6/14) of the double-blind trials. Some of the deficiencies in the published studies outlined above have been addressed in the recommendations of a committee on reporting standards in vascular surgery (Rutherford *et al* 1997) and it was noted in this review that sample sizes have tended to be higher in more recent studies, but there is still considerable room for improvement.

Currently there are few trials which have demonstrated an effect of adjuvant pharmacotherapy on peripheral graft patency in an adequately powered, multicentre, randomised, double-blind, placebo-controlled design. The current widespread use of aspirin and coumarins to maintain the patency of infra-inguinal bypass grafts regardless of graft material is not therefore strongly supported by the published trials. The aspirin data is strongest in prosthetic grafts and data on coumarins strongest in vein grafts, but only the general reduction of cardiovascular events by aspirin justifies its current widespread use (Antiplatelet Trialists Collaboration 1994b).

2.4. An overview of the development of iloprost as an adjuvant medical treatment for the reduction of distal bypass graft failure

Iloprost

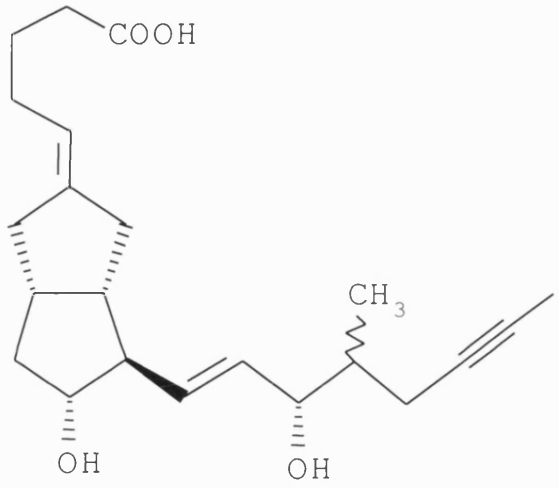
Chemical, pharmaceutical and pharmacological properties

Iloprost is a chemically stable analogue of the endogenous locally acting mediator, prostacyclin (PGI_2). The structure of the compounds is shown below (Figure 11).

Figure 11. Chemical structure of iloprost

ILOPROST; ZK 36 374

5-{(E)-(1S,5S,6R,7R)-7-Hydroxy-6-[(E)-(3S,4RS)-3-hydroxy-4-methyl-1-octen-6-ynyl]-bicyclo[3.3.0]oct-3-ylidene}-pentanoic acid



Iloprost is stable at room temperatures in a 1ml aqueous solution of 0.1 mg iloprost, 0.242mg Tris-(hydroxymethyl)-aminomethane (TRIS), 0.1N hydrochloric acid (to pH 8.3), 9.0mg sodium chloride and 0.01ml ethanol (96 vol.%). The drug is further dissolved in 500 ml of physiological saline for intravenous or intra-arterial infusion. Although chemically stable, the drug has a short biphasic plasma half-life with an α-phase of 3-4 minutes and a β-phase of 20-30 minutes after intravenous infusion. The metabolism of the drug is by β-oxidation of the α-side chain to form inactive metabolites. The principal pharmaceutical advantage of iloprost over prostacyclin is its chemical stability in solution. Prostacyclin needs to be stored in solid form, dissolved in a buffered solution at pH 5.5

and used within a few hours. Iloprost has the pharmacokinetic advantage that its plasma half-life is longer.

Iloprost has been shown to act as an agonist on the PGI_2 receptor with some additional less potent PGE_1-like activity. The pharmacological properties of iloprost relevant for its use in vascular disease include inhibition of platelet aggregation, dilation of peripheral arteries, reduction of activation of neutrophils and reduction of ischaemia-reperfusion injury in skeletal muscle (Belkin *et al* 1990, Schillinger *et al* 1986).

The minimum plasma concentration for pharmacological activity of iloprost in man has been demonstrated to be 100 pg/ml. This plasma level is achieved at steady state with an infusion of 0.5 ng iloprost/kg body weight/min. In a 70 kg man this dose corresponds to an infusion rate of 10 ml/h. For clinical studies infusion rates of 10 to 40 ml/h have been used with the upper limit, corresponding to 2.0 ng/kg/min, determined by the tolerance of acute side-effects. Typical dose-limiting side-effects are facial flushing, headache, diarrhoea, nausea, vomiting and hypotension. They are dose dependent and resolve rapidly on reduction of the infusion rate or termination of the infusion.

Studies indicating a desensitisation of platelet prostacyclin receptors to iloprost and prostacyclin after continuous infusion of more than 8 hours duration led to the adoption of a treatment regimen consisting of 6 to 8 hour daily infusions with a drug-free interval of 16-18 hours between infusions (Yardumian *et al* 1985, Sinzinger *et al* 1987). This practice also proved convenient for the daily working routine in the hospitals and allowed treatment on a day patient basis in some cases.

Previous clinical experience with iloprost

A number of large, multicentre, placebo-controlled clinical trials with intravenous iloprost in patients with severe peripheral arterial occlusive disease have shown benefit from daily 6 hour infusions for 14 to 28 days. Improved healing of ischaemic ulcers has been shown in both diabetic (Brock *et al* 1990) and non-diabetic patients (Diehm *et al* 1989) and relief of rest pain in both patients with and without trophic lesions (Bliss *et al* 1991, Balzer *et al* 1991). A reduction in major amputations and death in these patients has also been demonstrated (Bliss *et al* 1991, Loosemore *et al* 1994), but a large study investigating the healing of below-knee amputations failed to show any benefit of a 14-21 day treatment with iloprost (Dormandy *et al* 1994).

A number of smaller studies have been performed in patients with intermittent claudication using shorter treatment regimens, usually 3-5 days (Hay *et al* 1987, Müller-Bühl *et al* 1987, Wilkinson *et al* 1988). The studies have mostly failed to show any convincing benefit in this patient population.

Clinical trials have also been performed in a number of other indications including thromboangiitis obliterans (Fiessinger *et al* 1990), secondary Raynaud's phenomenon (McHugh *et al* 1988, Wigley *et al* 1994) and primary pulmonary hypertension (Dinh Xuan *et al* 1990) which have all shown clinical benefit with iloprost.

Rationale for the use of iloprost in distal bypass surgery

The benefit of iloprost treatment in patients with ischaemia of various origins is thought to be the result of a number of actions of iloprost including the reduction in platelet aggregation and vasospasm, improvement in microvascular perfusion and protection of the vascular endothelium.

It has been shown that there is a correlation between a high resistance to flow through the bypass graft and bypass failure. One component of the resistance in the early post-operative period may be a reduction in microcirulatory flow distal to the graft. This was thought to be potentially reversible or preventable by administration of iloprost during the operation. In addition, the administration of iloprost for a short period post-operatively might reduce graft failure through anti-thrombotic platelet inhibitory effects.

Objective of development plan

The objectives of the development plan were to investigate and obtain a marketing authorisation for peri-operative iloprost in femorodistal bypass grafts:

(1) by assessment of haemodynamic effects

(2) by establishing long-term influence on patency.

Patients studied

Patients studied were those undergoing femorodistal bypass surgery with the distal anastomosis on either the tibioperoneal trunk, the anterior or posterior tibial artery or the peroneal artery with the addition of patients having a below-knee popliteal anastomosis in one study.

The haemodynamic investigations were carried out only in patients with saphenous vein grafts, but patients receiving both vein and prosthetic grafts were included in the studies of bypass patency and the results analysed separately.

Steps in the development of iloprost

Dose finding for intraoperative administration

A dose escalation study was performed in twenty patients undergoing distal bypass surgery to investigate the tolerability and safety of iloprost and the dose response for improvement of graft blood flow (Shearman *et al* 1990). The doses used ranged from 50ng to 5μg iloprost given as a single short infusion (2-3 minutes) into the proximal end of the bypass graft after completion of the anastomoses and release of the arterial clamps. The drug was given via a cannula through an unligated side branch of the vein graft. Blood flow through the graft was recorded for 20 minutes by electromagnetic flow probe and systemic blood pressure was recorded via a radial artery cannula.

No measurable change in graft blood flow was recorded with doses from 50 to 750ng. Doses of 1μg and over produced an increase in flow. A dose response relationship was seen for graft blood flow for doses in the range 1μg to 5μg, but doses of 4μg and 5μg also led to a transient fall in systolic blood pressure of at least 30mmHg.

The 3μg dose was considered the optimum dose, producing a mean increase in blood flow of 128% 20 minutes after infusion without clinically significant effects on systolic blood pressure. The effect was quite dramatic in most cases with a visible increase in skin blood flow in the part of the limb distal to the bypass graft in contrast to the other leg (Figure 12).

Haemodynamic effects of intragraft administration

Two studies were performed to confirm the haemodynamic effects of intragraft iloprost studied by the comparison of iloprost 3μg and placebo (Hickey *et al* 1991, Smith *et al* 1992). Fifteen patients per treatment group were planned in each of the two randomised, double-blind parallel group design studies. Graft blood flow was measured by Doppler probe and distal resistance calculated.

Iloprost significantly increased graft blood flow for at least 20 minutes after injection by 94% and 52% compared to mean changes in the placebo groups of less than 10%. Mean distal resistance was decreased by 40% by iloprost for at least 20 minutes compared to a mean increase in the placebo group ($p<0.01$). Clinical follow-up of

patients showed a significant reduction in bypass occlusion after one month ($p<0.05$) in the patients from the two studies combined (Smith *et al* 1993).

Figure 12. Acute effect on skin blood flow of injection of iloprost into a distal bypass graft

Haemodynamic effects of additional post-operative infusion

A comparison was made of the haemodynamic effects of adding a post-operative iv or ia infusion or no post-operative infusion to intra-graft iloprost. Twenty-seven patients in an open, parallel-group design study were randomised into 3 groups:

- Intra-graft iloprost 3μg + post-operative 8 hour iv infusion up to 2.0 ng/kg/min
- Intra-graft iloprost 3μg + post-operative 8 hour ia infusion into the affected artery up to 0.5 ng/kg/min
- Intra-graft iloprost 3μg + no post-operative infusion

Graft blood flow was measured by Doppler probe and values during and after post-operative infusion compared with those at the end of the operation. Both post-operative intra-arterial ($p=0.006$) and intravenous ($p=0.05$) infusions increased blood flow during the infusion compared to the group receiving no post-operative iloprost infusion. Patients receiving post-operative intra-arterial infusions also had higher blood flow at the end of infusion compared to the patients not receiving any post-operative iloprost at the same time point, eight hours after surgery ($p=0.04$), but results in the group receiving intravenous infusions lay between the other two and were not significantly different from

either. Although the intra-arterial infusion gave the best haemodynamic effect, it was also associated with more practical problems such as graft infection and there was sometimes difficulty in finding a suitable side-branch for the cannula. The intravenous post-operative infusion was considered to be the preferred option as it appeared to offer a practical regimen to sustain the improvement in graft blood flow after the end of surgery.

In order to achieve a long-term improvement in graft patency, it was concluded that the best treatment regimen would be an intragraft infusion intra-operatively supplemented by daily intravenous infusions for as many days as was practicable post-operatively.

Long-term effects of a 3 day treatment regimen on bypass patency

The effects of iloprost on bypass patency were investigated in two multicentre, multinational, double-blind, placebo-controlled studies using a 3 day treatment regimen. The treatment comprised 3μg iloprost intragraft infusion intra-operatively and three 6 hour iv infusions given post-operatively with the addition of a one hour iv infusion at the start of surgery commencing after induction of anaesthesia. Bypass patency was assessed at the end of treatment, discharge from hospital (or 14 days, if sooner), 6 weeks, 3 months, 6 months and 12 months.

The number of patients included in the two studies were 517 and 175. The larger study showed no significant differences in vein graft primary patency over 12 months (iloprost 53%, placebo 52%), but showed a significant improvement in prosthetic graft primary patency at the end of treatment (iloprost 95%, placebo 74%, p=0.01), although not at 12 months (iloprost 46%, placebo 42%). Secondary patency results were similar. The results of this study are described in more detail (Chapter 4) and form the major part of this thesis as well as providing the basis for investigations of trial methodology.

The smaller of these two studies (Data on file, Schering AG, Berlin, 1997) also showed no significant difference in the vein graft primary patency at 12 months (iloprost 55%, placebo 42%), but there was a significant improvement in vein graft secondary patency at 12 months (iloprost 73%, placebo 54%, p=0.03). Differences in prosthetic graft patency were not significant.

These two studies suggest that although there may be some influence of iloprost on bypass patency, the long-term effects of a 3 day regimen may be too small or variable to be consistently apparent in studies of this size.

The methodology and results of the larger of these two studies form the basis of this thesis and are described and explored in more detail later.

Long-term effects of a 14 day treatment regimen on bypass patency

The effects on bypass patency of a 14 day regimen of iloprost were also investigated, but this study used an open design with patients allocated according to a randomisation schedule to receive either iloprost or heparin/saline infusions. Treatment consisted of 2-3 μg iloprost as an intra-graft infusion and a 6 hour iv infusion daily for 14 days post-operatively. Bypass patency was determined at the end of treatment, 3 months, 6 months and 12 months. The number of patients randomised was 424.

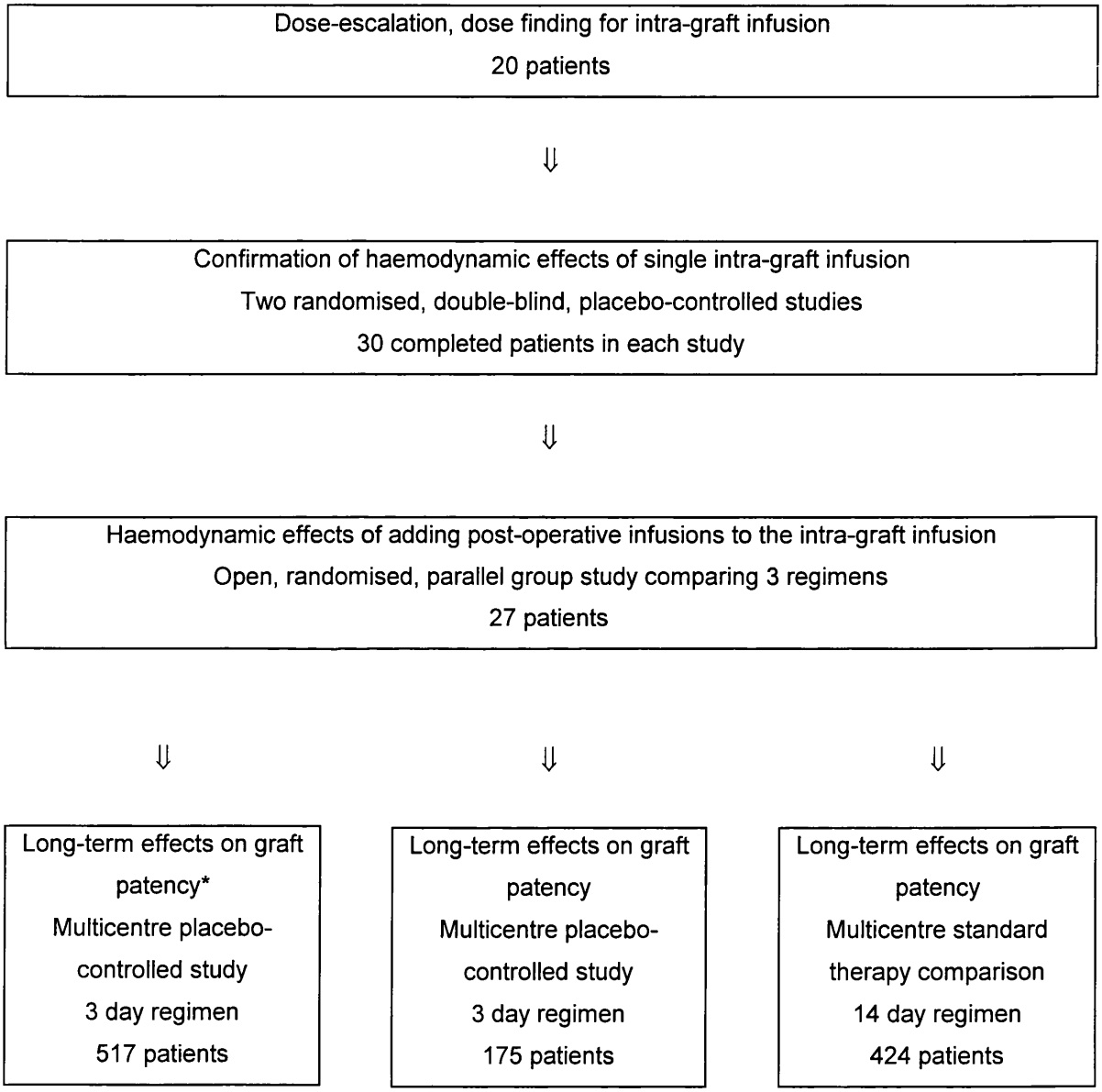
Primary and secondary patency rates were marginally higher in the iloprost group, but the differences were not statistically significant: primary patency in vein grafts at 12 months, iloprost 65%, placebo 63%. Although the study is open to criticism due to the lack of a double-blind design, these results were consistent with the conclusions drawn from the double-blind studies with the 3 day regimen.

Additional studies investigating mechanisms of action and use of iloprost in distal bypass procedures

Further clinical studies and investigation were performed with iloprost in peripheral bypass surgery in order to investigate pharmacological actions of the drug. These showed that platelet deposition in the vein graft and the distal vascular bed was not influenced by intra-operative administration (Smith *et al* 1992), but that capillary swelling in the distal microvasculature was reduced by the 3 day iloprost regimen (Thomson *et al* 1993).

The pharmacokinetics of the 3μg intra-graft administration were investigated and gave results comparable to those previously obtained with intravenous infusions. This confirmed that the prolonged action on distal resistance and graft blood flow was not the result of a longer than expected plasma half-life (Watson *et al* 1997). This study also showed an association of the systemic plasma concentration with the transient fall in systolic blood pressure seen in some patients.

Flow chart summarising main steps in the development plan



*Study described in this thesis

Discussion of development plan

There are a number of possible pitfalls in the investigation of potential adjuvant therapies in this indication: the choice of surrogate endpoint for early trials, dose-finding and the choice of treatment regimen, heterogeneity of patients and procedures, and the extrapolation of results of early trials to large multicentre trials.

Graft blood flow as a surrogate endpoint for bypass patency

Patency of the bypass graft as a clinical trial endpoint suffers from a number of disadvantages. Even in the relatively high risk group of patients receiving distal bypasses, occlusions do not occur with a high frequency in a short follow-up period. Any effect of therapy is also only of clinical relevance if it is sustained over at least 12 months. These two factors mean that treatment group sizes of over a hundred and follow-up periods of at least one year for all patients are necessary in order to demonstrate the effects likely to be seen with an adjuvant treatment. An intermediate or "surrogate" endpoint is therefore desirable and can be justified on practical, ethical and financial grounds.

There is currently no widely used or accepted surrogate endpoint for graft patency. This is partly due to the multifactorial nature of graft failure. Prevention of myointimal hyperplasia and graft stenosis will not help to predict the outcome of a graft in which the cause of failure is unsatisfactory runoff, for example.

In the development of iloprost as an adjuvant therapy, the intragraft dose, the route of administration post-operatively and the decision to investigate a long-term effect on graft patency were made on the basis of an effect on distal resistance and graft blood flow. In effect, these variables were used as surrogate endpoints. It has been suggested that the choice of a surogate endpoint should be based on three provisos (Boissel *et al* 1992). These are that the surrogate endpoint should be easier to assess (e.g. occurring more frequently than the clinical endpoint), that there should be a well established qualitative and quantitative relationship with the clinical endpoint and that it should be possible to derive an estimate of the expected clinical benefit from the change in the surrogate endpoint. These criteria undoubtedly represent the ideal situation, but will be difficult to satisfy in many disease areas, not least in bypass graft patency.

The first proviso is clearly satisfied in the case of iloprost and bypass patency, although the measurability of resistance is limited to the intra-operative period and post-operative measurement of graft blood flow is not very precise or reproducible.

Secondly, it is also clear that in the short term there is a qualitative relationship between graft blood flow and patency. If the graft is not patent, blood flow will be zero. To what extent blood flow is predictive of future patency and clinical improvement, however, is less clear. The hypothesis that pharmacological manipulation of outflow resistance and graft blood flow could lead to a increased likelihood of graft patency rested on the premise that an important component of the initial outflow resistance is amenable to long-term improvement. It was hypothesised that a certain proportion of patients suffer from a "low reflow" phenomenon after surgery as a consequence of the partial ischaemia during arterial clamping during the operation on top of the chronic ischaemic state of the lower limb. The mechanism of the low reflow phenomenon was suggested to be capillary swelling, vasopasm and luminal obstruction by activated neutrophils, a breakdown in the normal microvascular homeostatic mechanisms (Gidlof *et al* 1987). In contrast to the fixed component of the outflow resistance, due to the number of patent vessels distal to the bypass and the degree of stenosis in these vessels, the increased resistance due to the state of the microvasculature might be amenable to improvement.

Outflow resistance and graft blood flow have both been investigated for their association with graft patency. Ascer *et al* (1984) found that intra-operative measurement of outflow resistance was a good predictor of patency for up to 3 months and that transient reduction by papaverine was not associated with an improved likelihood of success. This association has been both confirmed (Davies *et al* 1993) and challenged (Peterkin *et al* 1988) by other studies. Investigations of intra-operative graft blood flow have shown that a very low volume flow (Dean *et al* 1975) and flow velocity (Bandyk *et al* 1985, Wilson *et al* 1988) are predictive of graft failure. The predictive value of angiographic runoff, in contrast seems to be more limited (Scott *et al* 1989).

The third criterion for accepting a surrogate endpoint is not met in this case beyond the finding that increasing blood flow above a certain critical level might open up a chance of a successful outcome. This, however, would just be supposition.

Iloprost is not the only agent which has been shown to give an immediate increase in blood flow through peripheral bypass grafts. Intra-arterial naftidrofuryl (Davies *et al* 1993), intra-arterial papaverine and oral nifedipine (Karacagil *et al* 1995) have all been shown to have a favourable short-term effect on graft haemodynamics. Epidural anaesthesia has also been shown to reduce peripheral resistance and increase graft blood flow after distal reconstructions (Hickey *et al* 1995). None of these agents , however, has been investigated for an effect on bypass patency and the effect of papaverine, at least, is known to be very transient (Parvin *et al* 1985). There is, therefore,

no confirmation from research with other agents that graft blood flow is a meaningful surrogate endpoint.

Studies showing graft blood flow and outflow resistance to be correlated with graft patency have generally concentrated on early graft failure up to one or three months. After this period development of graft stenosis is responsible for the failure of many vein grafts and graft thrombogenicity for the failure of prosthetic grafts. The magnitude of any effect of 3 days iloprost on graft stenosis development would be likely to be small and the antiplatelet effects of the drug are reversible and limited to the duration of infusion. A prolonged benefit of the peri-operative iloprost treatment up to one year would only be expected, therefore, if the whole patency-time curve is shifted upwards.

It could be concluded that early post-operative graft blood flow as a surrogate endpoint is probably useful only in predicting patency up to 3 months. Beyond this time other mechanisms of graft failure predominate and these may be influenced by other medication taken by the patients. Demonstrating a long-term shift in the patency curve on the basis of a treatment designed to improve early post-operative graft blood flow is likely to prove difficult. A combination of this approach with administration of long-term treatment to reduce the likelihood of thrombosis may be more successful.

Treatment regimen

The pattern of change in graft blood flow after peripheral bypass operations described by Cronenstrand *et al* (1970) showed that almost all patients have a maximum flow established through the graft two days after the operation and that most have achieved this after 24 hours. The first placebo-controlled study suggested that a single intra-operative administration of iloprost might be enough to give a prolonged improvement in graft blood flow. Although a second study showed a trend in the same direction, the data were less convincing and suggested a tailing off of the effect over the first few post-operative days. Consequently, it was decided to extend the duration of iloprost treatment by giving additional post-operative infusions. This had the additional theoretical advantage of affording the patients the benefit of an anti-thrombotic effect from the inhibition of platelet aggregation by iloprost. However, there was no real dose-finding study performed with the post-operative infusions in this indication.

A comparison of the risks and benefits of different routes of administration post-operatively indicated that the intra-arterial route, although giving the greatest enhancement of graft blood flow, exposed the patient to additional hazards which were probably not justified by the potential benefit. There was a concern that the systemic plasma levels of iloprost resulting from intravenous infusion might lead to a reduction in

graft blood flow due to a steal effect. There was no evidence of this, however, and the intravenous infusion group showed a maintenance of the high graft blood flow produced by the intra-graft injection when compared to the group receiving no post-operative iloprost. The 3 day treatment duration was decided upon for purely practical reasons. It was thought to be advantageous to give iloprost for as long as possible, but there were practical limitations on the duration. Patients are generally mobilised as early as possible after distal bypass surgery making intravenous infusions an inconvenience and it is policy in some centres to transfer patients to a convalescent hospital within 5 days of the bypass operation. Three days was the longest period for which it could be guaranteed that all patients would receive uninterrupted treatment.

It is conceivable that a longer period of treatment might have yielded a greater benefit. The results of the study with 14 days treatment suggest, however, that continuous treatment might be necessary to exert a meaningful effect. This would be dependent on the availability of an oral or other more convenient dosage form. Even the 14 day infusion regimen was accepted by medical staff and ethics committees only in an open study, so that patients in the control group did not have to be kept in hospital unnecessarily. This aspect of the design of this study unfortunately also reduces the value of the results, as it opened the possibility of bias in the allocation of patients to treatment groups, choice of additional therapy and assessment of clinical outcome.

The use of an intermittent infusion regimen consisting of daily 6 hour infusions was based on small clinical pharmacology studies showing a desensitisation of platelets to the inhibitory effect of iloprost and a possible hyperaggregability with sustained infusions (Yardumian *et al* 1985). Despite the theoretical risk this entails, no adverse clinical sequelae of prolonged iloprost infusions have been attributed to a prothrombotic effect of this kind of administration even with continuous infusion of patients with primary pulmonary hypertension for many months. It is perhaps indicative of the importance given to risk avoidance in pharmaceutical development that continuous infusions were not investigated in this indication, although the principal desired effects, reduction in distal resistance and improvement in graft performance, had not been shown to be best achieved by an intermittent infusion regimen. There were theoretically possible beneficial effects of to be derived from a sustained inhibition of platelet function. These include reduced likelihood of thrombosis and reduced release of platelet derived growth factor, which has been implicated in myointimal hyperplasia in vein grafts. However, an objective assessment of the demonstrated haemodynamic benefits and the likely risks might conclude that a continuous post-operative intravenous infusion held the greatest potential for improving the outcome of distal bypass surgery.

Patient selection

The choice of patients undergoing femorodistal bypass surgery as a target group was based on the unsatisfactory success rate of the procedures and the perception that there was an early post-operative problem in many cases. Femoropopliteal bypasses, in contrast, particularly those to the above-knee popliteal artery usually have a better run-off and have a much higher success rate with mid-term development of graft stenosis the major cause of graft failure. Long bypasses to the dorsalis pedis carry a particularly high risk of failure, but are relatively seldom performed and do not, therefore, make an easy study population.

The primary interest was to investigate the effect of iloprost in vein grafts. These make up the majority of distal bypasses performed. Prosthetic and vein prosthetic composite grafts, which are less often used due to their higher failure rate below the knee, were thought to be a less attractive target group for short-term iloprost treatment since the problem of thrombogenicity of these grafts is not limited to the immediate post-operative period. The early dose-ranging and haemodynamic studies were performed only in patients with vein grafts for these reasons.

The inclusion of both vein and prosthetic grafts in the multicentre studies of graft patency was unavoidable due to the adoption of a treatment regimen beginning shortly after induction of anaesthesia. At this stage in the operation it is not always clear whether it will be possible to use the patient's own vein for a bypass or whether it will be necessary to use exogenous material. Having already started treatment with the study drug when this becomes known, the choice for the study designer is to stop treatment of all the patients with prosthetic grafts and exclude them from the analysis, or to continue the treatment and follow-up and analyse the data from all patients. This latter course was chosen, but with the decision being made *a priori* to analyse the outcome of vein and prosthetic grafts separately. This was based on the knowledge that the predominant causes of graft failure may differ in vein and prosthetic grafts and the efficacy of a drug could not, therefore, be assumed to be the same in both types of surgical procedure.

Statistical power

The two larger studies designed to investigate effects on graft patency were both intended to have 80% power (with an α=0.05) to show an improvement in patency at 12 months from an estimated 75% in the control group to 88% in the iloprost group. The smaller patency study had sufficient power only to show a greater difference in patency rates and was planned with the intention of using the data in a meta-analysis if no

difference was found in this study alone. The differences in all studies were in favour of iloprost, but were smaller than the studies were designed to detect. The question of whether the numerical differences seen are likely to represent a real difference in the treatments could be answered only by further larger studies or by a meta-analysis of the data from all studies.

Influences on drug development within the pharmaceutical industry

Any analysis of a drug development programme must take into account the various influences which contribute to shaping the development. Medical science, the prior knowledge of the drug's properties and the pathophysiology of the condition being treated, are only some of these influences. In the case of iloprost as adjuvant therapy in distal bypass it could be argued that medical science points to a likely effect of the drug in high risk cases.

Distinct from medical science is clinical need. The need in this case is for a therapy which has an impact on long-term outcome. Here the desires of the clinicians and the marketing departments in the pharmaceutical industry coincide. They both want to see a long-term effect. Where these two parties may diverge in this indication is in the choice of target population. The clinicians will usually attach the highest priority to improving outcome of those cases at greatest risk of failure, the prosthetic grafts or the more problematic vein grafts. The marketing departments in contrast would tend to prefer a drug to be used more widely, for example in all distal bypasses, and would therefore like trials to be conducted in a broader group of patients. A wider use helps to meet the pharmaceutical industry's need to recoup development costs.

A further influence on drug development is time. This is not only because drugs in development cost the company money and drugs on the market may earn money. The inexorable progress towards the expiry of the patent on a drug means that the rewards are potentially greater with an earlier conclusion to a development programme. This time pressure often translates into proceeding on the strength of incomplete information to the next stage in the development. An example in the iloprost development would be the adoption of a treatment regimen for large scale studies which had only partly been tested in dose-finding studies in this indication.

In an ideal development programme, the intra-operative dose-finding and the choice of dose-regimen would have been more extensively investigated. A more limited aim of improving short-term outcome in a more carefully selected high-risk group of patients might also have led to a more successful outcome.

Summary

Following careful review of the literature and of the clinical programme described, it was felt desirable to consider how trial design in this area might be improved. The next two chapters, chapters 3 and 4, describes the methods and results of the main trial with iloprost in detail. These include further analyses performed on this database in order to investigate potential improvements in trial design and the determination of outcome.

3. METHODS

Contribution of the author to planning and execution of the study

The author was responsible for discussing the results of earlier studies with iloprost (described in section 2.4) with a small number of leading vascular surgeons in order to determine what evidence would be needed to establish the efficacy of a drug in the maintenance of distal bypass patency. Having decided on the need for a large study with bypass patency as the primary endpoint, the author proposed a study design and protocol which was finalised after discussion with the same small group of clinicians.

The next stages were to design the record forms for data collection and to select appropriately experienced surgical centres for the trial. The author was also responsible for writing an explanation of the trial for patients and for ensuring that the necessary regulatory and ethics committee approvals were obtained for each participating centre. The surgeons were then responsible for enrolling patients into the trial.

During the enrolment and follow-up of the patients, the author's role was to supervise a team of data monitors who visited each site at regular intervals in order to validate the data being recorded and to take any decisions on questions about the conduct of the study which were not answered by the protocol. These mostly concerned the suitability of certain patients for inclusion in the trial and the acceptability of unanticipated surgical procedures or concomitant medications.

The author worked together with a statistician to agree a statistical analysis plan for the data generated and subsequently to agree on the interpretation of the results. This analysis, performed by the statistician, covered the principal comparison of iloprost and placebo treatment groups described. The analyses subsequently performed on the database and described in the later sections of the results chapter were planned and performed by the author.

Study design

The design of the study was a double blind, randomised, prospective, multicentre trial for the comparison of two parallel treatment groups, iloprost and placebo. There was an assessment of the patients one day before treatment, a treatment period of three days duration including the day of surgery and a post treatment follow-up period of 12 months. The study design is illustrated in Figure 13. Patients were recruited in 21 vascular surgical centres from six countries in Northern Europe (Denmark, Ireland, the Netherlands, Norway, Sweden and the United Kingdom). Data collection was monitored from a co-ordinating centre and validated by reference to original data sources such as hospital records. The protocol was submitted to and approved by the appropriate Ethics

Committee for each of the participating centres and by the regulatory authorities with the responsibility for research into new medicines in the respective countries.

Patient were recruited into the study over an 18 month period between September 1990 and March 1992. Clinical follow-up of the patients was completed a further 12 months later in March 1993.

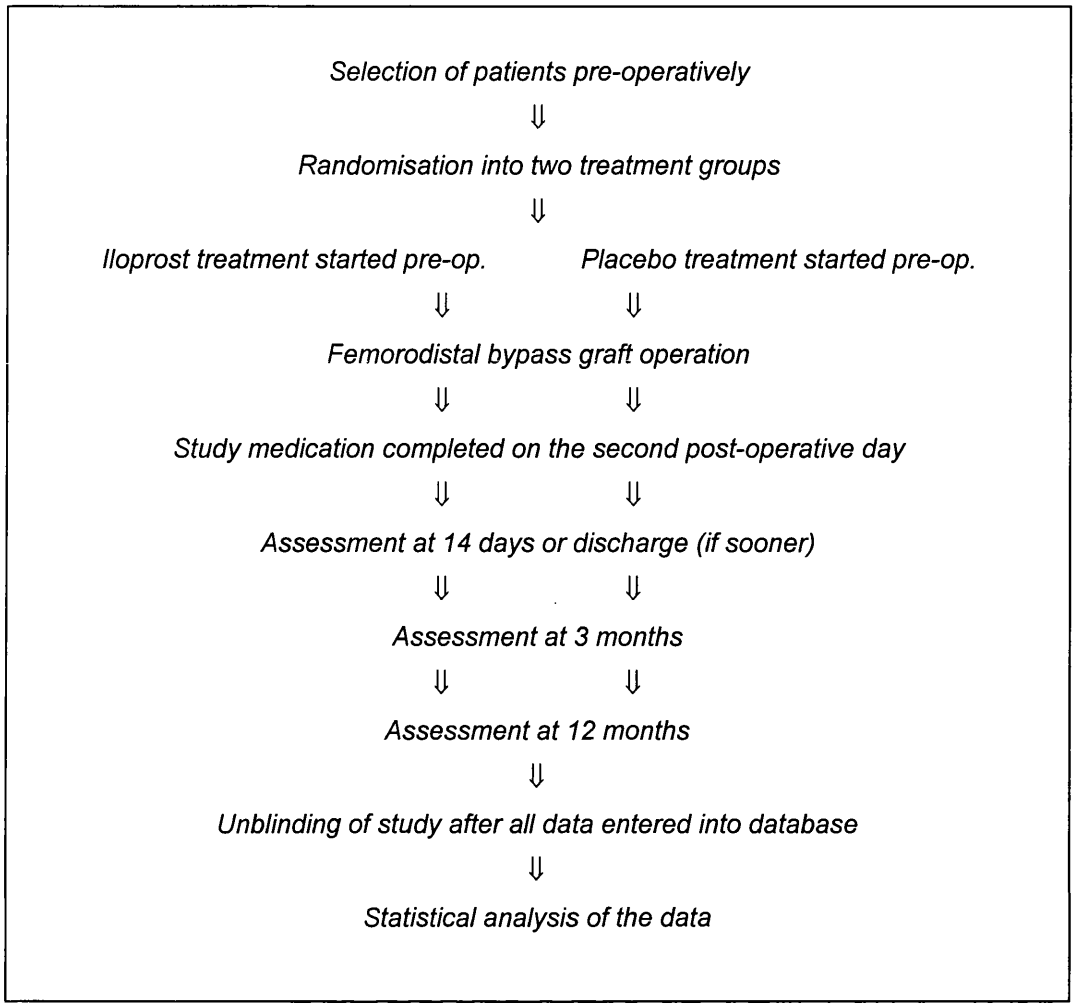
Selection of patients

It was planned to study patients undergoing bypass surgery for critical ischaemia with the proximal anastomosis above the knee and the distal anastomosis to the tibioperoneal trunk, the anterior tibial, posterior tibial or peroneal artery. Critical ischaemia was defined as: 1) the presence of trophic lesions or 2) persistent rest pain requiring analgesia for at least two weeks plus an ankle pressure of less than 50mmHg, except in the case of patients with diabetes mellitus and calcified arteries where absent palpable foot pulses were accepted as sufficient evidence of severe vascular disease. This was in accordance with the recommendations of the Second Consensus Document of the European Working Group on Critical Limb Ischaemia (1991). Patients with only intermittent claudication (PAOD Fontaine stage II) or a planned distal anastomosis proximal to the origin of the anterior tibial artery were not to be included.

Specific criteria for exclusion of patients for safety reasons were known deficient haemostatic function (except where this was the result of treatment with oral anticoagulant drugs), active gastrointestinal bleeding and a history of intracranial bleeding).

Both male and female patients were included. Informed consent was obtained from all patients according to the requirements of the Declaration of Helsinki (Hong Kong, 1989). Consent was obtained pre-operatively and no study-specific procedures were performed on the patients before consent had been obtained. Patients not giving consent to participation were not randomised and no data on these patients was recorded in the study files.

Figure 13. Flow chart of study design



Randomisation procedure

Randomisation of the patient to one of the two treatment groups was stratified by centre and performed in the following manner. Each trial centre was given a sequence of randomisation numbers in blocks of ten, e.g. 01-10, 11-20. Each block of ten numbers contained an equal number of iloprost and placebo treatments.

Appropriate patients were identified pre-operatively. When a patient satisfied the entry criteria, the clinician gave the patient the next available number in the sequence. This number corresponded with a treatment box containing the iloprost or placebo treatment. Each treatment box contained ampoules labelled with the study number and randomisation number and nothing to distinguish the iloprost from the placebo ampoules without the randomisation code. For each randomisation number the clinician also had a sealed envelope containing the treatment allocation. The envelope was only to be

opened in the case of emergency where knowledge of the treatment received would help the management of the patient.

The generation of the randomisation schedule was performed by an independent statistician using a computer random number generation programme. The randomisation schedule was known only to this statistician and to the pharmacist responsible for labelling the study medication appropriately. The study manager, hospital staff, data monitors, data entry staff, the statistician who performed the analysis and the patients were not aware of the treatment allocation.

Adjuvant drug treatment

Iloprost was supplied as one millilitre ampoules clearly identified with the name of the manufacturer, protocol number and patient trial number. The ampoules contained 0.1mg iloprost per millilitre in a sterile 0.9% NaCl solution with the addition of TRIS buffer. A box containing five ampoules was provided for each patient in the study. Those ampoules containing placebo were labelled in the same way and contained all of the aforementioned excipients.

One millilitre ampoules of iloprost or placebo were diluted into 500 ml of physiological saline. The treatment consisted of an intravenous infusion up to 20 ml/h for 1 hour starting after induction of anaesthesia, an injection of 15 ml into the proximal end of the bypass graft on completion of the procedure but before skin closure, a 6 hour infusion up to 20 ml/h starting 1 hour after the end of the operation and a further 6 hour intravenous infusion on each of the two following days up to a maximum of 40 ml/h. The treatment schedule is illustrated in Table 17.

The intravenous infusions at the beginning of the operation and post-operatively were given via a peripheral line to an arm vein. The infusions were titrated up starting at 10 ml/h in increments of 10 ml/h at 30 minute intervals to a maximum of 20 ml/h or 40 ml/h as described. Systemic haemodynamics and side-effects were monitored during the infusions. The increase in dose was stopped if side-effects such as headache, nausea or muscular cramps supervened and, if necessary, the infusion rate was reduced in steps of 10 ml/h to a more tolerable level. The tolerated dose was then maintained to the end of the stipulated infusion period. A reduction in doses usually allows a rapid resolution of any side-effects, but if any of the following symptoms occurred, it was recommended to interrupt the infusion until the situation normalised and then to continue at no more than half of the flow rate. These were a clinically significant decrease in blood pressure, an increase in heart rate above 130 / min. or a vagal reaction with bradycardia, nausea or vomiting.

The injection of 3000 ng of iloprost or placebo into the bypass graft was performed after completion of the anastomoses, after removal of the arterial clamps and after a completion angiogram, if one was performed. The injection, consisting of 15 ml of the solution, was given slowly over a period of 1-2 minutes in order to minimise the acute effect on systemic haemodynamics. In the case of vein grafts, the injection was given through an unligated vein branch near the proximal end of the graft left for this purpose. In the case of prosthetic grafts, the injection was given either through the wall of the graft with a fine needle or intra-arterially proximal to the graft provided that the femoral profunda artery was clamped to ensure delivery of the drug through the graft.

The infusion rates of 20 ml/h and 40 ml/h were planned to be equivalent in the average patient to iloprost doses of 1.0 and 2.0 ng/kg/min, assuming a 67 kg body weight, and the intra-graft injection of 15 ml was equivalent to a dose of 3000 ng iloprost.

Table 17. Summary of treatment schedule

Day	Procedures
1: Day of operation	• An iv infusion of study medication given for 30 minutes immediately after induction of anaesthesia and stabilisation of the patient. • An injection of 15ml of study medication given slowly into the bypass graft after establishing blood flow through the graft. • One 6 hour iv infusion of study medication started 1 hour after end of operation.
2: 1st post-operative day	• One 6 hour iv infusion of study medication.
3: 2nd post-operative day	• One 6 hour iv infusion of study medication.

Concomitant medications

Peripheral vasodilators for the treatment of critical limb ischaemia were stopped two weeks before surgery and were not permitted during the treatment period of the study. Papaverine, however, was allowed for diagnostic purposes during the operation. Analgesics for the treatment of ischaemic pain were continued as required.

Heparin, oral anticoagulants and dextrans were used both during and after treatment with the study substance according to each centre's policy provided that their use was recorded. The use of aspirin and other platelet aggregation inhibitors was not permitted during the three days of study treatment, but was allowed thereafter according to the policy of each individual centre. Peripheral vasodilators and other drugs for the

treatment of critical ischaemia were not allowed during the study. All concomitant medications were recorded.

Pre-operative assessment

Demographic data, past medical history, concurrent illnesses, risk factors and medication being taken by the patient were recorded pre-operatively. In addition to recording patient's height and weight, the body mass index and body surface area were calculated according to the following formulas:

Body mass index was calculated according to the formula:

Body mass index in kg/m^2 = weight in kg / height in $metres^2$.

Body surface area was calculated according to the Dubois formula:

Body surface area in cm^2 = $\sqrt{}$(body weight in kg x height in cm x 167.2).

Clinical status was assessed as shown in Table 18 and according to these symptoms, the patient was classified according to Fontaine in stages I to IV of peripheral arterial occlusive disease. Each of the ischaemic symptoms were assigned a numerical score depending on severity as shown in the last column of Table 18 and these were summated to produce a single numerical value between 0 and 6 representing the presence and overall severity of ischaemic symptoms.

Table 18. Assessment of clinical status

Parameter	Categories	Score
Rest pain in the previous 24 hours	None	0
	Intermittent	1
	Continuous	2
Analgesic use in the previous 24 hours	None	0
	Non-opiate alone	1
	Opiate with or without non-opiate	2
Ischaemic ulcers	Absent	0
	Present	1
Gangrene	Absent	0
	Dry	1
	Wet	1
	Dry and wet	1

Ankle and brachial Doppler pressures were recorded pre-operatively. Ankle-brachial pressure index (ABPI) was calculated. Angiographic run-off was calculated using a method which takes into account both the number and state of the vessels distal to the graft (Rutherford *et al* 1986). The run-off was scored between 1 and 10 where 1 represents excellent outflow and 10 represents no outflow.

Surgical procedures and post-operative management

Technical details of the operation were recorded. These included the leg operated, the type of anaesthesia (general, epidural, intradural, local nerve block), location of the proximal and distal anastomoses in terms of vessel and level, graft length and minimum graft diameter, graft material. Concomitant vascular procedures such as endarterectomy in the region of the anastomosis, profundaplasty, the use of a vein cuff or patch to improve the distal anastomosis and arterio-venous fistulae were also recorded, as were the intra-operative use of angiography, Doppler, Duplex or endoscopy techniques and the need for revision of either the proximal or distal anastomoses during the operation.

Information on the post-operative management of the patients recorded included the use of glucose and electrolyte infusions, blood transfusion requirements, antiplatelet and anticoagulant treatment, graft complications and oedema formation.

Postoperative follow-up

Post-operative follow-up on all patients was 12 months. Graft patency, clinical symptoms and Doppler pressures were recorded at 2 days, 3 days, 14 days (or discharge if sooner), 3 months and 12 months. Assessments of graft patency at 6 weeks and 6 months and graft surveillance by duplex ultrasound at all time-points were optional. Graft stenoses were considered to be clinically significant if the ratio of blood flow velocity at the point of greatest stenosis was at least twice that at another point within 2 cm. The method of measurement is described below.

Clinical status and Doppler pressures were assessed in the same manner as pre-operatively. Further vascular interventions in the relevant leg including amputations were recorded whenever they occurred. The classification of these is described below.

Definition of patency and amputation levels

Primary patency was defined as patency of the graft without any further intervention after skin closure in the initial bypass operation. Further intervention to improve bypass function without the graft having first occluded led to a definition of assisted primary patency, for example if a dilatation of a vein graft stenosis was performed. Successful

intervention after graft occlusion led to secondary patency. Secondary patency was classified as being achieved primarily by surgical or pharmacological intervention. Patency of the bypass graft had to be confirmed either by angiography or Duplex ultrasound.

Revision of the anastomoses during the original bypass operation before administration of the study drug into the graft and before skin closure was not classified as a loss of primary patency if it occurred before the patient left the operating theatre. Loss of primary patency occurred only when the bypass occluded or had to be revised to avoid occlusion after skin closure at the end of the initial bypass operation. Analysis of secondary patency rates followed the convention of including all patients with primary, assisted primary and secondary patency. Similarly, calculation of assisted primary patency rates included all patients with primary and assisted primary patency.

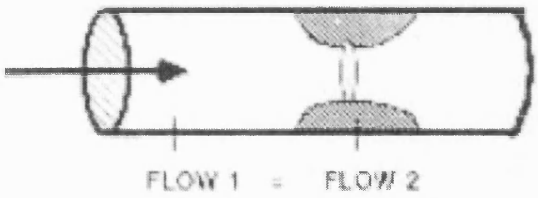
Amputations were classified as major or minor. Major amputations were defined as above-knee, through-knee or below-knee amputations in which the ankle joint was not retained. Minor amputations were those in which the ankle joint was retained.

Definition of graft stenoses

Graft stenoses were detected by the method of Grigg *et al* (1988) in which areas of high velocity flow within the graft are identified by Duplex scanning along the entire length of the graft. The presence of a graft stenosis was defined by an increase in peak systolic velocity of >50% over a distance of <2cm along the graft. That is, where V_2=velocity at the site of stenosis and V_1=velocity in an unstenosed portion of the graft within 2cm of the stenosis, the ratio $V_2 : V_1$ should be >1.5.

The $V_2 : V_1$ ratio and % stenosis were recorded together with confirmation of the stenosis by intravenous digital subtraction angiography. The relationship of stenosis to velocity change is illustrated below (Figure 14) and rests upon the fact that flow in terms of volume per unit time must be the same at each point along the vessel and that it is the product of the cross-sectional area and velocity at that point.

Figure 14. Derivation of % stenosis from velocity changes where V_1 is the velocity at an unstenosed section of the graft and V_2 is the velocity at the stenosis



volume flow = cross-sectional area (A) x velocity (V)

$V_2 / V_1 = A_1 / A_2$

$V_2 / V_1 = r_1^2 / r_2^2$

$r_2 = \sqrt{(r_1^2 \times V_1 / V_2)}$

% stenosis = $(r_1 - r_2) / r_1 \times 100$

% stenosis = $100 \times [1 - \sqrt{(V_1 / V_2)}]$

Haemodynamic measurements

In addition to ankle pressures measured by Doppler and the calculation of ABPI, duplex ultrasound was used to measure the peak systolic flow velocity in a non-stenosed section approximately halfway along the graft. The cross-sectional area of the graft was measured and an estimate of mean volume flow through the graft was calculated. These duplex assessment of graft function were optional and not performed by all centres.

Adverse events

All adverse medical events were recorded on the basis that it is not always clear which events can be attributed to the treatment under test and accurately described as side-effects. Events were recorded on each day of treatment. At the time of discharge and at subsequent follow-up visits, adverse medical events which had occurred in the intervening period were recorded.

On the basis of previous studies the possibility of an acute transient effect on blood pressure was known (Hickey *et al* 1991). Blood pressure and heart rate were

monitored throughout the administration of the study medication and for a short period after each infusion.

Unexpected medical events occurring in the per-operative and post-operative periods could also be recorded as surgical complications or as graft complications if they were felt to be primarily a result of the surgical procedure.

Summary of assessment schedule

Table 19. Timing of assessments

Assessments	Admi-ssion	Opera-tion / day 1	Day 2	Day 3	Disch-arge / Day 14	6 weeks	3 month	6 weeks	12 month
Demographic	X								
Concurrent illness & medication	X	X	X	X	X				
Operative & post-op management		X	X	X	X				
PAOD symptoms	X		X	X	X		X		X
Angiography	X	X							
Haemodynamics	X	X	X	X	X		X		X
Graft patency			X	X	X	(X)	X	(X)	X
Graft stenoses						(X)	(X)	(X)	(X)
Adverse events		X	X	X	X		X		X

Footnote: X = assessment required, (X) = assessment optional

Data collection and management

Data were recorded in triplicate on self-copying case report forms specially designed for the study. The three copies of the report forms provided an original for the study co-ordinating centre, a copy for the study site and a copy for data entry. The completion of the forms was monitored according to Good Clinical Practice guidelines and a proportion of the data on the forms was checked against the entries in the patient's hospital notes for accuracy. The items checked for all cases included patient's identification, surgical

procedures and the principal outcome parameters of patency, amputation and death. Entries in the case report forms were made and altered only by the clinical staff at the centres.

Visits were made to monitor the data on site prior to collection at six to eight weekly intervals. Monitoring was performed by the study manager (the author) or by experienced clinical trial monitors from the study co-ordinating centre, which was independent of any of the participating surgical centres. The total duration of the data collection phase of the study was 27 months.

The data entry and analysis was performed in a blinded fashion. All data were entered twice by different data entry clerks and checked automatically for consistency of the two entries as well as for internal consistency of data on the same patient from different examination dates. Prior to data entry, a plausibility check was programmed, so that any implausible data would automatically be rejected unless checked and reconfirmed. A final manual check of a sample of the data was performed before locking the database and breaking the randomisation code to analyse the data.

Manipulation and analysis of the data was performed using SigmaStat® statistical software version 2.03 for Windows® 95 (Jandel Scientific Software GmbH, Erkrath, Germany). Graphical displays were generated using SigmaPlot® version 4.0 (Jandel Scientific Software GmbH, Erkrath, Germany). The operating system used was Windows® 95 (Microsoft, Inc., United States).

Statistical considerations

The primary efficacy variable selected for the trial was primary patency of the bypass graft (definition given earlier in this section). It was planned to analyse the patients according to graft material, with the primary analysis of interest being the analysis of patients with vein grafts. The study sample size was chosen based on the ability to detect an absolute difference of 12.5% in primary patency rates between iloprost and placebo. Literature review prior to the start of the study suggested cumulative primary patency in vein grafts in the control group to be 75%, which resulted in a hypothesised 87.5% cumulative patency rate for the iloprost group. Calculations were based on a test of independent proportions performed with $\alpha = 0.05$ and $\beta = 0.10$. A total of 221 evaluable patients were required per treatment group to demonstrate a difference in patency rate between the iloprost and placebo groups.

Statistical analyses were performed on all available data for all patients (intention to treat) for whom graft patency could be assessed. Patients were divided into two groups for the analysis of patency data: those receiving vein grafts and those receiving

grafts partly or wholly consisting of prosthetic material. Bypass patency, vascular intervention, amputation and survival curves were based on Kaplan-Meier product-limit estimates, and overall differences between pairs of curves were compared using log-rank tests. Data were grouped according to assessment intervals for patency and in monthly intervals for interventions, amputations and deaths. Actuarial (life-table) estimates are more commonly used for grouped data, but Kaplan-Meier and life-table estimates are nearly identical for these data.

Thirty day months were assumed and conversions to months were used in the calculation and analysis of cumulative patency rates (Table 20).

Table 20. Time points used in the calculation of cumulative patency rates

Time point	**Months**
1st day post-operation	0.033
2nd day post-operation	0.067
3rd day post-operation	0.10
Discharge or 14 days	0.47
6 weeks	1.50
3 months	3.00
6 months	6.00
12 months	12.00

Missing values due to death or amputation before loss of patency or loss to follow up are all counted as censored data and not treated as failures in the calculation of Kaplan-Meier product limit estimates. The analysis makes use of this censoring procedure to estimate the true rates which would be evident if all patients were evaluable throughout the entire follow-up period.

Distribution of the data were assessed for normality using the Kolmogorov-Smirnov test (with Lilliefors' correction). Results are expressed as mean ± standard deviation for normally distributed variables and as medians and ranges for non-normal data. Comparisons of categorical variables and continuous variables were aided by the calculation of 95% confidence intervals. Confidence intervals for event rates were calculated according to the following formula:

$$95\%\ CI = 1.96 \times \sqrt{(rate(1-rate)/n)}$$

where the rate is the number of events or number of patients divided by the number of patients in the group.

Handling of withdrawals

Non-evaluable withdrawals were those patients randomised with the intention of performing a bypass operation, but who were found to be unsuitable for a bypass graft for technical reasons. Patients randomised, but for whom no data was recorded were not included in the evaluation.

Patients who withdrew from the study of their own volition or who discontinued study medication on the advice of the clinician were followed up as far as possible according to the study protocol. All available data on patients who died or underwent amputation of the leg before bypass occlusion were evaluated.

4. RESULTS

Efficacy and safety of peri-operative iloprost in a placebo controlled trial in femorodistal bypass surgery

4.1 Description of patients

Disposition of patients

Over a two year period 528 patients were randomised into the study. Eleven were excluded after randomisation. Of these eleven, eight were found to be unsuitable for bypass on commencement of the operation and did not undergo the planned bypass procedure. The other three of those excluded after randomisation received the study medication, but had no data recorded in the case report forms making classification and analysis of these cases impossible. This resulted in 517 patients being available for analysis of bypass patency, 267 randomised to iloprost and 250 to the placebo group. Twenty-one centres contributed patients to the study. The number of cases entered by individual centres varied between 1 and 100 with a median of 17 patients per centre.

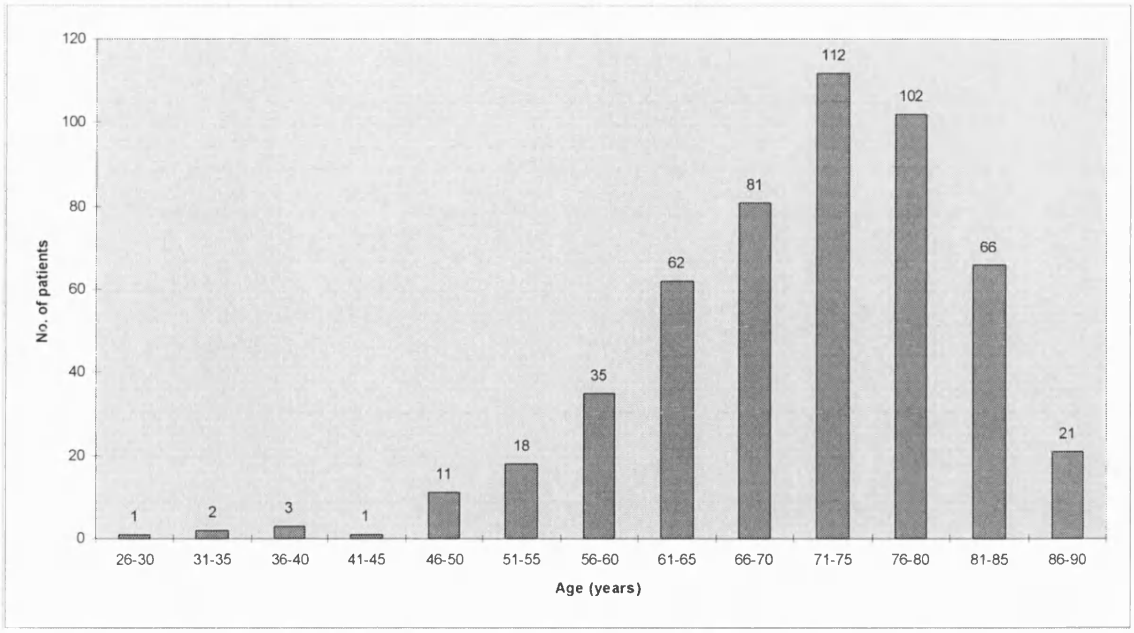
Demographic characteristics of patients

The 517 patients consisted of 317 males and 199 women (and 1 unclassified) with a mean age of 71.2 years (Figure 15). Female patients comprised 110 (41.2%) of the iloprost group and 90 (36.0%) of the placebo group. The demographic characteristics of the two treatment groups did not differ significantly (Table 21).

Table 21. Demographic characteristics (mean ± standard deviation)

Characteristic	Iloprost (n=267)	Placebo (n=250)	Total (n=517)
Age (years)	71.2 ± 9.4 n=267	71.2 ± 10.3 n=250	71.2 ± 9.9 n=517
Height (cm)	169 ± 10 n=220	170 ± 10 n=213	169 ± 10 n=433
Weight (kg)	68.6 ± 14 n=249	70.9 ± 14 n=241	69.7 ± 14 n=490

Figure 15. Distribution of age in the study population



The distribution of the patients' pre-operative general clinical characteristics (Table 22) shows that the two treatment groups were generally well matched with respect to a number of concurrent clinical conditions and risk factors which might have had a bearing on the clinical outcome.

Table 22. Pre-operative clinical characteristics

Characteristic	Number of patients (%)					
	Iloprost (n=267)		Placebo (n=250)		Total (n=517)	
Hypertension	60	(22.5)	63	(25.2)	123	(23.8)
Diabetes mellitus	99	(37.1)	85	(34.0)	184	(35.6)
Hyperlipidaemia	16	(6.0)	18	(7.2)	34	(6.6)
Cardiac failure	25	(9.4)	18	(7.2)	43	(8.3)
Previous MI	58	(21.7)	59	(23.6)	117	(22.6)
Previous CVA	31	(11.6)	26	(10.4)	57	(11.0)
Mobility restricting illness	9	(3.4)	15	(6.0)	24	(4.6)
Other severe accompanying illness	41	(15.4)	38	(15.2)	79	(15.3)
Current smoker	89	(33.3)	94	(37.6)	183	(35.4)

Pre-operative arterial disease

Patients' arterial disease was classified as Fontaine stage III (34%) or Fontaine stage IV (65.2%) in all but four cases. The distribution of patients into the two treatment groups was quite well balanced with respect to stage and duration of symptoms with just a small excess of patients in stage IV in the iloprost group (Table 23).

Table 23. Pre-operative Fontaine stage and duration of symptoms

Fontaine stage	Number of patients (%)		
	Iloprost (n=267)	Placebo (n=250)	Total (n=517)
Stage II	3 (1.1)	1 (0.4)	4 (0.8)
Stage III	84 (31.5)	92 (36.8)	176 (34.0)
Stage IV	180 (67.4)	157 (62.8)	337 (65.2)
Duration of stage III	4.4 ± 6.4 years	4.5 ± 5.0 years	4.4 ± 5.7 years
Duration of stage IV	5.0 ± 6.4 years	4.8 ± 5.0 years	4.9 ± 5.8 years

Rest pain was reported in 499 patients (96.5%), but only 406 patients (78.5%) were receiving any analgesia (Table 24). There was a greater proportion of patients with both ulcers and necroses in the iloprost group than in the placebo group: 85 patients (31.8%, 95%CI 26.2-37.4) compared to 55 patients (22.0%, 95%CI 16.9-27.1) (Table 25).

Table 24. Pre-operative rest pain and analgesic use

Rest pain	Analgesic	Number of patients (%)		
		Iloprost (n=267)	Placebo (n=250)	Total (n=517)
None	None	8 (3.0)	2 (0.8)	10 (1.9)
	Non-opiates	3 (1.1)	4 (1.6)	7 (1.4)
	Opiates	0 (0.0)	1 (0.4)	1 (0.2)
Intermittent	None	46 (17.2)	29 (11.6)	75 (14.5)
	Non-opiates	40 (15.0)	54 (21.6)	94 (18.2)
	Opiates	25 (9.4)	26 (10.4)	51 (9.9)
Continuous	None	14 (5.2)	12 (4.8)	26 (5.0)
	Non-opiates	70 (26.2)	63 (25.2)	133 (25.7)
	Opiates	61 (22.8)	59 (23.6)	120 (23.2)

Table 25. Pre-operative ulcers and gangrene

Ulcers	Gangrene	Number of patients (%)					
		Iloprost (n=267)		Placebo (n=250)		Total (n=517)	
Absent	None	87	(32.6)	92	(36.8)	179	(34.6)
	Dry	33	(12.4)	38	(15.2)	71	(13.7)
	Wet	3	(1.1)	1	(0.4)	4	(0.8)
	Dry and wet	3	(1.1)	3	(1.2)	6	(1.2)
Present	None	56	(21.0)	60	(24.0)	116	(22.4)
	Dry	56	(21.0)	32	(12.8)	88	(17.0)
	Wet	17	(6.4)	11	(4.4)	28	(5.4)
	Dry and Wet	12	(4.5)	12	(4.8)	24	(4.6)

The overall symptom severity scores did not differ greatly between the two groups with median values of 4.0 for the iloprost group (IQ range 2.0-5.0) and 3.0 for the placebo group (IQ range 2.0-5.0).

Arterial pressures were similar in the two groups: the mean overall ankle pressure recorded in the relevant leg was 56.2 mmHg with 188 patients (36.4%) having a pressure of < 50 mmHg and the mean ABPI was 0.37 with 462 cases (89.3%) being ≤ 0.6 (Table 26).

Table 26. Pre-operative Doppler pressures

Variable	Iloprost		Placebo		Total	
Brachial artery	152 ± 26	(n=261)	153 ± 27	(n=246)	153 ± 27	(n=507)
Ankle: mean ± SD	58 ± 44	(n=243)	55 ± 38	(n=223)	56 ± 41	(n=466)
< 50mmHg	96	(36%)	92	(37%)	188	(36%)
≥ 50mmHg	147	(55%)	131	(52%)	278	(54%)
ABPI: mean ± SD	0.65 ± 0.33	(n=251)	0.65 ± 0.32	(n=236)	0.65 ± 0.32	(n=487)
0 - 0.30	34	(14%)	29	(12%)	63	(13%)
0.31-0.60	83	(33%)	87	(37%)	170	(35%)
0.61 - 0.90	81	(32%)	64	(27%)	145	(30%)
> 0.90	53	(21%)	56	(24%)	109	(22%)

Angiographic run-off scores in the two groups were similar (Table 27). Insufficient information from the angiograms on the distal vessels did not permit the calculation of a run-off scores in approximately 15% of cases.

Table 27. Pre-operative angiographic run-off score (Rutherford system)

	Number of patients (%)		
Run-off score	Iloprost (n=267)	Placebo (n=250)	Total (n=517)
0 - 2.0	52 (19.5)	58 (23.2)	110 (21.3)
2.5 - 4.0	60 (22.5)	47 (18.8)	107 (20.7)
4.5 - 6.0	34 (12.7)	38 (15.2)	72 (13.9)
6.5 - 8.0	39 (14.6)	27 (10.8)	66 (12.8)
8.5 - 10.0	41 (15.4)	41 (16.4)	82 (15.9)
Invalid score	41 (15.4)	39 (15.6)	80 (15.5)

4.2 Surgical procedures

The duration of surgery was a mean of 4.0 hours (range 2.0-8.5) in all patients and did not differ either between the treatment groups or between those patients undergoing bypass with vein and prosthetic grafts (Table 28).

Table 28. Duration of surgery (hours) by treatment group and by graft material

Graft material	Statistic	Iloprost	Placebo
All patients	mean ± SD	3.9 ± 1.4	4.0 ± 1.3
	range	1.5 ± 11.0	2.0 - 8.5
	n	267	250
Vein grafts	mean ± SD	3.8 ± 1.3	4.1 ± 1.3
	range	1.5 - 10.0	2.0 - 8.0
	n	209	215
Prosthetic grafts	mean ± SD	4.1 ± 1.9	4.0 ± 1.3
	range	1.5 - 11.0	2.0 - 8.5
	n	57	35

General anaesthesia with or without epidural was used in 287 cases (55.5%), epidural alone in 198 (38.3%) and intradural (3.7%) or local nerve blocks (2.5%) in the remainder. The frequency of use of the different types of anaesthesia was similar in the two treatment groups and with the different types of graft material used (Table 29).

Table 29. Numbers of patients operated under each type of anaesthesia

Graft material	Type of anaesthesia	Iloprost number (%)	Placebo number (%)	Totals number (%)
All patients	General	150 (56.2)	137 (54.8)	287 (55.5)
	Epidural	100 (37.5)	98 (39.2)	198 (38.3)
	Intradural	10 (3.7)	9 (3.6)	19 (3.7)
	Local	7 (2.6)	6 (2.4)	13 (2.5)
Vein grafts	General	115 (55.0)	112 (52.1)	227 (53.5)
	Epidural	80 (38.3)	90 (41.9)	170 (40.1)
	Intradural	9 (4.3)	8 (3.7)	17 (4.0)
	Local	5 (2.4)	5 (2.3)	10 (2.4)
Prosthetic grafts	General	35 (60.3)	25 (71.4)	60 (64.5)
	Epidural	20 (34.5)	8 (22.9)	28 (30.1)
	Intradural	1 (1.7)	1 (2.9)	2 (2.2)
	Local	2 (3.4)	1 (2.9)	3 (3.2)

The proximal anastomosis was most commonly made to the common femoral artery, femoral bifurcation or proximal superficial femoral artery (SFA) (438 cases (84.8%)) and only rarely to the mid superficial femoral artery or above-knee popliteal artery (Table 30). Prosthetic grafts were anastomosed to the common femoral artery more frequently than vein grafts and rarely to the mid SFA, femoral profunda or above-knee popliteal artery, reflecting a tendency to place prosthetic grafts more proximally. Iloprost and placebo groups were well-matched in the frequency of the various sites of proximal anastomosis.

Table 30. Site of proximal anastomosis

	Number of patients (%)					
Artery	Iloprost		Placebo		Total	
All grafts						
Iliac	3	(1.1)	3	(1.2)	6	(1.2)
Common femoral	147	(55.1)	144	(57.6)	291	(56.3)
Femoral bifurcation	36	(13.5)	30	(12.0)	66	(12.8)
Proximal superficial femoral	43	(16.1)	38	(15.2)	81	(15.7)
Femoral profunda	5	(1.9)	7	(2.8)	12	(2.3)
Mid superficial femoral	18	(6.7)	16	(6.4)	34	(6.6)
Above-knee popliteal	14	(5.2)	12	(4.8)	26	(5.0)
Not recorded / not done	1	(0.4)	0	(0.0)	1	(0.2)
Vein grafts						
Iliac	1	(0.5)	1	(0.5)	2	(0.5)
Common femoral	103	(49.3)	117	(54.4)	220	(51.9)
Femoral bifurcation	30	(14.4)	27	(12.6)	57	(13.4)
Proximal superficial femoral	39	(18.7)	37	(17.2)	76	(17.9)
Femoral profunda	5	(2.4)	5	(2.3)	10	(2.4)
Mid superficial femoral	17	(8.1)	16	(7.4)	33	(7.8)
Above-knee popliteal	14	(6.7)	12	(5.6)	26	(6.1)
Not recorded / not done	1	(0.5)	0	(0.0)	1	(0.2)
Prosthetic grafts						
Iliac	2	(3.5)	2	(5.7)	4	(4.3)
Common femoral	44	(77.2)	27	(77.1)	71	(77.2)
Femoral bifurcation	6	(10.5)	3	(8.6)	9	(9.8)
Proximal superficial femoral	4	(7.0)	1	(2.9)	5	(5.4)
Femoral profunda	0	(0.0)	2	(5.7)	2	(2.2)
Mid superficial femoral	1	(1.8)	0	(0.0)	1	(1.1)
Above-knee popliteal	0	(0.0)	0	(0.0)	0	(0.0)

The distal anastomoses were distributed evenly between the anterior tibial, posterior tibial and peroneal arteries in both treatment groups with a smaller proportion on the tibioperoneal trunk (Table 31). Although not falling within the inclusion criteria of the study, a small number of patients with a distal anastomosis on the below-knee popliteal artery or on the dorsalis pedis artery were entered.

Table 31. Sites of distal anastomoses

Artery	Level of distal anastomosis (no. of patients (%))							
	Upper		Mid		Lower		Totals	
Below-knee popliteal	9	(1.8)	0	(0.0)	0	(0.0)	9	(1.8)
Tibioperoneal trunk	40	(7.7)	2	(0.4)	2	(0.4)	44	(8.5)
Anterior tibial	56	(10.8)	53	(10.3)	70	(13.5)	179	(34.6)
Posterior tibial	22	(4.3)	57	(11.0)	65	(12.6)	144	(27.9)
Peroneal	46	(8.9)	55	(10.6)	38	(7.4)	139	(26.9)
Dorsalis pedis	0	(0.0)	0	(0.0)	2	(0.4)	2	(0.4)
All vessels	173	(33.5)	167	(32.3)	177	(34.2)	517	(100.0)

The distribution of different vessels for the distal anastomosis in the two treatment groups was well balanced (Table 32).

The distal anastomoses were also evenly distributed between the upper, mid and lower thirds of the calf vessels in the study population as a whole and in the patients receiving vein grafts without any differences between the two treatment groups (Table 33). Amongst patients who received prosthetic grafts, more in the iloprost group, 33.3% (95%CI 21.1-45.5), than in the placebo group, 17.1% (95%CI 4.6-29.6), were anastomosed to the distal third of the calf vessels, but this difference between the treatment groups was not significant.

Vein grafts, including composite grafts from two sections of vein, were used in 424 cases (82%) and prosthetic or prosthetic-vein composite grafts in 92 (18%) (Table 34). The *in situ* technique was used in 68.9% of the vein grafts performed, 21.2% of vein grafts were reversed vein grafts and 9.9% were composite grafts consisting of two pieces of vein. Of the prosthetic grafts, 67.4% were simple PTFE grafts and 31.5% were composite grafts part vein and part PTFE. A greater proportion of the prosthetic grafts were performed in the iloprost group, 21.3% (95%CI 16.2-26.2), compared to the placebo group, 14.0% (95%CI 9.7-18.3).

Table 32. Site of distal anastomosis

Artery	Number of patients (%)					
	Iloprost		Placebo		Total	
All grafts						
Below-knee popliteal	7	(2.6)	2	(0.8)	9	(1.7)
Tibio-peroneal trunk	20	(7.5)	24	(9.6)	44	(8.5)
Anterior tibial	94	(35.2)	85	(34.0)	179	(34.6)
Posterior tibial	75	(28.1)	69	(27.6)	144	(27.9)
Peroneal	70	(26.2)	69	(27.6)	139	(26.9)
Dorsalis pedis	1	(0.4)	1	(0.4)	2	(0.4)
Vein grafts						
Below-knee popliteal	5	(2.4)	1	(0.5)	6	(1.4)
Tibio-peroneal trunk	14	(6.7)	18	(8.4)	32	(7.5)
Anterior tibial	76	(36.4)	75	(34.9)	151	(35.6)
Posterior tibial	61	(29.2)	60	(27.9)	121	(28.5)
Peroneal	52	(24.9)	60	(27.9)	112	(26.4)
Dorsalis pedis	1	(0.5)	1	(0.5)	2	(0.5)
Prosthetic grafts						
Below-knee popliteal	2	(3.5)	1	(2.9)	3	(3.3)
Tibio-peroneal trunk	6	(10.5)	6	(17.1)	12	(13.0)
Anterior tibial	18	(31.6)	10	(28.6)	28	(30.4)
Posterior tibial	14	(24.6)	9	(25.7)	23	(25.0)
Peroneal	17	(29.8)	9	(25.7)	26	(28.3)
Dorsalis pedis	0	(0.0)	0	(0.0)	0	(0.0)

Table 33. Level of distal anastomosis in the calf

	Number of patients (%)					
Level on calf artery	Iloprost		Placebo		Total	
All grafts						
Upper third	91	(34.1)	86	(34.4)	177	(34.2)
Mid third	80	(30.0)	84	(33.6)	164	(31.7)
Lower third	95	(35.6)	80	(32.0)	175	(33.8)
Unknown	1	(0.4)	0	(0.0)	1	(0.2)
Vein grafts						
Upper third	73	(34.9)	71	(33.0)	144	(34.0)
Mid third	60	(28.7)	70	(32.6)	130	(30.7)
Lower third	76	(36.4)	74	(34.4)	150	(35.4)
Prosthetic grafts						
Upper third	18	(31.6)	15	(42.9)	33	(35.9)
Mid third	20	(35.1)	14	(40.0)	34	(37.0)
Lower third	19	(33.3)	6	(17.1)	25	(27.1)

Table 34. Graft material

Graft material	Number of patients (%)					
	Iloprost (n=267)		Placebo (n=250)		Totals (n=517)	
In situ saphenous vein	141	(52.8)	151	(60.4)	292	(56.5)
Reversed saphenous vein	47	(17.6)	43	(17.2)	90	(17.4)
PTFE	39	(14.6)	23	(9.2)	62	(12.0)
Other prosthetic	0	(0)	1	(0.4)	1	(0.2)
Vein-prosthetic composite	18	(6.7)	11	(4.4)	29	(5.6)
Vein-vein composite	21	(7.9)	21	(8.4)	42	(8.1)
Unclassified	1	(0.4)	0	(0)	0	(0.2)

Information on the graft length was recorded for 62.1% of grafts (321 patients), 63.9% of vein grafts and 54.3% of prosthetic grafts. The mean graft length was similar in both treatment groups (Table 35). Minimum graft diameters were recorded for 71.2% of grafts (368 patients), 71.7% of vein grafts and 69.5% of prosthetic grafts (Table 36). The minimum graft diameters in patients receiving vein bypasses were not evenly distributed

and were somewhat smaller in the iloprost group than the placebo group: 3.7mm (95%CI 3.5-3.9) and 4.0mm (95%CI 3.8-4.2) respectively.

Table 35. Graft length (cm)

Graft material	Statistic	Iloprost	Placebo
All patients	mean ± SD	57.1 ± 14.2	58.0 ± 13.9
	range	14.0 - 92.0	15.0 - 90.0
	n	164	157
Vein grafts	mean ± SD	57.0 ± 15.1	57.6 ± 14.1
	range	14.0 - 92.0	15.0 - 90.0
	n	134	137
Prosthetic grafts	mean ± SD	57.6 ± 9.8	60.6 ± 11.7
	range	32.0 - 74.0	42.0 - 80.0
	n	30	20

Table 36. Minimum graft diameter (mm)

Graft material	Statistic	Iloprost	Placebo
All patients	mean ± SD	4.1 ± 1.3	4.2 ± 1.5
	range	2.0 - 8.0	2.0 - 11.0
	n	192	176
Vein grafts	mean ± SD	3.7 ± 1.0	4.0 ± 1.4
	range	2.0 - 7.0	2.0 - 11.0
	n	152	152
Prosthetic grafts	mean ± SD	5.5 ± 1.1	5.7 ± 1.1
	range	2.0 - 8.0	3.0 - 8.0
	n	40	24

Concomitant procedures were performed in similar numbers of cases in each treatment group (Table 37). Endarterectomy and profundaplasty were most commonly performed in patients receiving vein bypasses. Amongst prosthetic bypass grafts, procedures to improve the haemodynamics at the distal anastomosis were performed in the majority of operations and with equal frequency in the two treatment groups. Vein collars or cuffs were used in about 40% of cases and vein patches such as the Taylor patch were used in

almost 20% of cases. Arteriovenous fistulae were performed rarely and only at one centre participating in the trial.

Table 37. Concomitant surgical procedures at time of bypass procedure

	Number of patients (%)					
Concomitant procedure	Iloprost		Placebo		Total	
All grafts						
Endarterectomy	46	(17.2)	43	(17.2)	89	(17.2)
Profundaplasty	11	(4.1)	9	(3.6)	20	(3.9)
Miller collar	24	(9.0)	16	(6.4)	40	(7.7)
Taylor or other vein patch	14	(5.2)	13	(5.2)	27	(5.2)
Arteriovenous fistula	7	(2.6)	4	(1.6)	11	(2.1)
Vein grafts						
Endarterectomy	40	(19.1)	40	(18.6)	80	(18.9)
Profundaplasty	10	(4.8)	9	(4.2)	19	(4.5)
Miller collar	2	(1.0)	1	(0.5)	3	(0.7)
Taylor or other vein patch	3	(1.4)	6	(2.8)	9	(2.1)
Arteriovenous fistula	2	(1.0)	1	(0.5)	3	(0.7)
Prosthetic grafts						
Endarterectomy	6	(10.5)	3	(8.6)	9	(9.8)
Profundaplasty	1	(1.8)	0	(0.0)	1	(1.1)
Miller collar	22	(38.6)	15	(42.9)	37	(40.2)
Taylor or other vein patch	11	(19.3)	7	(20.0)	18	(19.6)
Arteriovenous fistula	5	(8.8)	3	(8.6)	8	(8.7)

Techniques used for intra-operative assessment of the patients included angiography, measurement of Doppler pressures, duplex ultrasound and endoscopy. The frequency of use of these different techniques was similar in the two treatment groups and showed that intra-operative assessment was performed principally with angiography and Doppler measurements (Table 38). Endoscopy was rarely performed in this study and only at one centre.

Table 38. Intra-operative assessments

	Number of patients (%)					
Type of assessment	Iloprost		Placebo		Total	
All grafts						
Angiography	152	(56.9)	131	(52.4)	283	(54.7)
Doppler	168	(62.9)	160	(64.0)	328	(63.4)
Duplex	15	(5.6)	15	(6.0)	30	(5.8)
Endoscopy	6	(2.2)	1	(0.4)	7	(1.4)
Vein grafts						
Angiography	114	(54.5)	114	(53.0)	228	(53.8)
Doppler	141	(67.5)	148	(68.8)	289	(68.2)
Duplex	14	(6.7)	14	(6.5)	28	(6.6)
Endoscopy	6	(2.9)	1	(0.5)	7	(1.7)
Prosthetic grafts						
Angiography	38	(66.7)	17	(48.6)	55	(59.8)
Doppler	27	(47.4)	12	(34.3)	39	(42.4)
Duplex	1	(1.8)	1	(2.9)	2	(2.2)
Endoscopy	0	(0.0)	0	(0.0)	0	(0.0)

Intra-operative graft revision was performed in 44 operations (8.5%), usually at the distal anastomosis (Table 39). The frequency of revisions was similar in the two treatment groups, but was twice as common in prosthetic bypass procedures as in veins. Other intra-operative technical complications were reported in a total of 67 cases (13.0%): iloprost 32 cases (12.0%) and placebo 35 cases (14.0%).

Surgeons' assessment of prognosis at the end of the operation were good for over two thirds of patients and tended to be rather more positive for patients with vein grafts than prosthetic grafts (Table 40). Very few patients were considered to be in imminent danger of amputation at the end of the operation.

Table 39. Frequency of intra-operative graft revision

	Number of patients (%)					
Site of revision	Iloprost		Placebo		Total	
All grafts						
Any revision	24	(9.0)	20	(8.0)	44	(8.5)
Proximal	3	(1.1)	4	(1.6)	7	(1.4)
Distal	18	(6.7)	15	(6.0)	33	(6.4)
Proximal and distal	3	(1.1)	0	(0.0)	3	(0.6)
Mid-graft	0	(0.0)	1	(0.4)	1	(0.2)
Vein grafts						
Any revision	15	(7.2)	16	(7.4)	31	(7.3)
Proximal	2	(1.0)	3	(1.4)	5	(1.2)
Distal	11	(5.3)	12	(5.6)	23	(5.4)
Proximal and distal	2	(1.0)	0	(0.0)	2	(0.5)
Mid-graft	0	(0.0)	1	(0.5)	1	(0.2)
Prosthetic grafts						
Any revision	9	(15.8)	4	(11.4)	13	(14.1)
Proximal	1	(1.8)	1	(2.9)	2	(2.2)
Distal	7	(12.3)	3	(8.6)	10	(10.9)
Proximal and distal	1	(1.8)	0	(0.0)	1	(1.1)
Mid-graft	0	(0.0)	0	(0.0)	0	(0.0)

The operations were performed by the principal surgeon in the group in over seventy percent of cases and by a junior or training surgeon in the remainder (Table 41). In the event that more than one surgeon was involved this reflects the surgeon who performed the distal anastomosis. Markedly more of the prosthetic grafts overall were performed by the principal surgeon of group than was the case for the vein grafts. This trend was similar in both treatment groups. The frequency of the prosthetic grafts being performed by the principal surgeon was higher in the placebo group, 91.4% (95%CI 82.1-100), than it was in the iloprost group, 80.7% (95%CI 70.5-90.9).

Table 40. Subjective assessment of prognosis

	Number of patients (%)					
Assessment of prognosis	Iloprost		Placebo		Total	
All grafts						
Good	186	(69.7)	176	(70.4)	362	(70.0)
Doubtful	65	(24.3)	65	(26.0)	130	(25.1)
Danger of amputation	13	(4.9)	9	(3.6)	22	(4.3)
Unknown	3	(1.1)	0	(0.0)	3	(0.6)
Vein grafts						
Good	156	(74.6)	155	(72.1)	311	(73.3)
Doubtful	44	(21.1)	53	(24.7)	97	(22.9)
Danger of amputation	6	(2.9)	7	(3.3)	13	(3.1)
Unknown	3	(1.4)	0	(0.0)	3	(0.7)
Prosthetic grafts						
Good	30	(52.6)	21	(60.0)	51	(55.4)
Doubtful	21	(36.8)	12	(34.3)	33	(35.9)
Danger of amputation	7	(12.3)	2	(5.7)	9	(9.8)
Unknown	0	(0.0)	0	(0.0)	0	(0.0)

Table 41. Surgeon performing operation

	Number of patients (%)					
Surgeon	Iloprost		Placebo		Total	
All grafts						
Principal surgeon	197	(73.8)	178	(71.2)	375	(72.5)
Assistant surgeon	70	(26.2)	72	(28.8)	142	(27.5)
Vein grafts						
Principal surgeon	151	(72.2)	146	(67.9)	297	(70.0)
Assistant surgeon	58	(27.8)	69	(32.1)	127	(30.0)
Prosthetic grafts						
Principal surgeon	46	(80.7)	32	(91.4)	78	(84.8)
Assistant surgeon	11	(19.3)	3	(8.6)	15	(15.2)

4.3 Administration of study medication and adverse medical events

The majority of patients received the planned treatment of iloprost or placebo. The infusion of study medication at the start of the operation was given to 506 patients (97.9%) and the intra-graft injection of iloprost or placebo to 498 (96.4%). Post-operatively 222 iloprost patients (83.1%) and 212 placebo patients (84.8%) received all three intravenous infusions. Six iloprost patients (2.2%) and 6 placebo patients (2.4%) did not receive any post-operative treatment with the study medication.

The planned infusion rate of 20 ml/h for the intravenous infusion given at the start of the operation was administered to 85% of patients overall, most of the remainder receiving an infusion at a rate of 10 ml/h (Table 42).

Table 42. Highest flow rate of intra-operative intravenous infusion and volume of intragraft injection

	Dose administered	Iloprost number	(%)	Placebo number	(%)	Total number	(%)
Intravenous infusion	0 ml/h	4	(1.5)	7	(2.8)	11	(2.1)
	10 ml/h	35	(13.1)	31	(12.4)	66	(21.8)
	20 ml/h	228	(85.4)	212	(84.8)	440	(85.1)
Intragraft injection	0 ml	7	(2.6)	11	(4.4)	18	(3.5)
	15 ml	257	(96.3)	235	(94.0)	492	(95.2)
	>15 ml	2	(0.7)	4	(1.6)	6	(1.2)

Over the three days of post-operative infusions, progressively more patients required a reduction in the infusion rate or stopped treatment completely (Table 43). A small number of patients (13 patients, 2.5%) on the first day also received an infusion at a higher dose than the 20 ml/h required by the protocol. However, the majority of patients received the planned infusion on each of the first three days of postoperative treatment. There were no major differences between the two treatment groups in the proportions of patients requiring dose reduction or cessation of treatment.

Table 43. Flow rate of post-operative infusions of study treatment

Infusion time	Dose administered	Iloprost number	(%)	Placebo number	(%)	Total number	(%)
Day 1	0 ml/h	7	(2.6)	9	(3.6)	16	(3.1)
	10 ml/h	11	(4.1)	4	(1.6)	15	(2.9)
	20 ml/h	242	(90.6)	231	(92.4)	473	(91.5)
	30 ml/h	2	(0.7)	3	(1.2)	5	(1.0)
	40 ml/h	5	(1.9)	3	(1.2)	8	(1.5)
Day 2	0 ml/h	22	(8.2)	20	(8.0)	42	(8.1)
	10 ml/h	3	(1.1)	6	(2.4)	9	(1.7)
	20 ml/h	10	(3.7)	6	(2.4)	16	(3.1)
	30 ml/h	14	(5.2)	4	(1.6)	18	(3.5)
	40 ml/h	218	(81.6)	214	(85.6)	432	(83.6)
Day 3	0 ml/h	41	(15.4)	37	(14.8)	78	(15.2)
	10 ml/h	6	(2.2)	5	(2.0)	11	(2.1)
	20 ml/h	12	(4.5)	6	(2.4)	18	(3.5)
	30 ml/h	18	(6.7)	10	(4.0)	28	(5.4)
	40 ml/h	190	(71.2)	192	(76.8)	382	(73.9)

Intra-operative adverse events

Considerably more iloprost patients had side-effects during the operation: 18.0% (95%CI 13.4-22.6) compared to 5.2% (95%CI 2.4-8.0) had any adverse event. The most common of these was hypotension: iloprost 39 patients (14.6%, 95%CI 10.2-18.8) and placebo 10 patients (4.0%, 95%CI 1.6-6.4). There were no significant differences in any other intra-operative events although (Table 44) vomiting occurred exclusively in the iloprost group, in 5 cases (1.9%, 95%CI 1.3-3.5) suggesting the possibility that this may be an uncommon iloprost-related event.

Table 44. Intra-operative adverse events

Adverse experience	Iloprost number (%) n = 267	Placebo number (%) n = 250
One or more	48 (18.0)	13 (5.2)
Hypotension	39 (14.6)	10 (4.0)
Nausea	6 (2.2)	2 (0.8)
Vomiting	5 (1.9)	0 (0.0)
Haemorrhage	2 (0.7)	0 (0.0)
Chest pain	2 (0.7)	0 (0.0)
Oedema	1 (0.4)	0 (0.0)
Lung oedema	1 (0.4)	0 (0.0)
Bigeminy	1 (0.4)	0 (0.0)
Headache	1 (0.4)	0 (0.0)
Myocardial infarction	1 (0.4)	0 (0.0)
Injection site inflammation	1 (0.4)	0 (0.0)
Flushing	1 (0.4)	0 (0.0)
Cardiovascular disorder	0 (0.0)	1 (0.4)
Hypoxia	0 (0.0)	1 (0.4)
Increased sweating	0 (0.0)	1 (0.4)

The incidence of hypotension during surgery (as judged by the clinician) did not differ greatly between patients operated under general anaesthesia and those receiving epidural anaesthetics (Table 45). In each case episodes of hypotension were significantly more common in patients receiving iloprost, 15.7% (95%CI 8.6-22.8), than placebo, 3.0% (95%CI 0-6.3%), and there was no indication of an interaction between the type of anaesthesia and the study treatment. The numbers of cases operated under intradural or local anaesthesia were too small to allow a valid comparison to be made. Similarly, the number of reports of other adverse events intra-operatively were too few to enable any judgement of relative frequency with general or epidural anaesthesia (Table 44). The single case of myocardial infarction during surgery occurred in a patient under epidural anaesthesia receiving iloprost and two additional cases of chest pain during surgery were reported in patients under epidural anaesthesia, one in each treatment group.

Table 45. Incidence of intra-operative hypotension (as judged by clinician) by treatment group and by type of anaesthesia

Type of anaesthesia	Iloprost Number (%)	Placebo Number (%)	Total Number (%)
General	20 (13.2) n=151	5 (3.6) n=140	25 (8.6) n=291
Epidural	16 (15.7) n=102	3 (3.0) n=100	19 (9.4) n=202

Recorded changes in systemic haemodynamics during surgery also indicated a higher incidence of hypotension in the iloprost group, showing a higher frequency of decreases in systolic and diastolic pressure both after the intravenous infusion at the beginning of the operation and after intra-graft injection at the end of the bypass procedure (Table 46 and 47). Heart rate was also increased, but only after the intravenous infusion, not after intra-graft injection (Table 48).

Table 46. Changes in blood pressure after intravenous infusion at the start of the operation

Change in blood pressure (mmHg)		Iloprost n=265 Number	% (95%CI)	Placebo n=245 Number	% (95%CI)
Systolic pressure	+ >30	10	4 (2-6)	6	3 (1-5)
	+ 11-30	27	10 (6-14)	37	15 (11-20)
	± 0-10	132	50 (44-56)	144	59 (53-65)
	− 11-30	67	25 (20-30)	36	15 (10-19)
	− >30	29	11 (7-15)	22	9 (5-13)
Diastolic pressure	+ >30	0	0	3	1 (0-2)
	+ 11-30	25	10 (6-13)	20	8 (5-11)
	± 0-10	168	66 (60-72)	189	78 (73-83)
	− 11-30	53	21 (16-26)	28	12 (8-16)
	− >30	9	4 (2-6)	3	1 (0-3)

Table 47. Changes in blood pressure after intragraft injection

Change in blood pressure (mmHg)		Iloprost n=252 Number	%	(95%CI)	Placebo n=238 Number	%	(95%CI)
Systolic pressure	+ >30	1	0	(0-1)	1	1	(0-1)
	+ 11-30	8	3	(1-5)	22	9	(5-13)
	± 0-10	108	43	(37-49)	179	75	(69-81)
	– 11-30	80	32	(26-38)	33	14	(10-18)
	– >30	55	22	(17-27)	3	1	(0-3)
Diastolic pressure	+ >30	0	0		0	0	
	+ 11-30	4	2	(0-3)	8	3	(1-5)
	± 0-10	172	70	(64-76)	212	90	(86-94)
	– 11-30	68	28	(22-33)	16	7	(4-10)
	– >30	2	1	(0-2)	0	0	

Table 48. Changes in heart rate after intra-operative treatment

Change in heart rate (mmHg)		Iloprost n=252 Number	%	(95%CI)	Placebo n=238 Number	%	(95%CI)
Intravenous infusion	+ >15	15	6	(3-9)	8	3	(1-5)
	± 0-15	221	83	(79-88)	228	93	(90-96)
	– >15	29	11	(7-15)	9	4	(1-6)
Intragraft injection	+ >15	8	3	(1-5)	1	0	(0-1)
	± 0-15	240	95	(93-98)	234	99	(97-100)
	– >15	4	2	(0-3)	2	1	(0-2)

The hypotensive effect of iloprost after the intra-operative intravenous infusion was evident from systolic and diastolic blood pressure measurements only in patients under general anaesthesia (Table 49 and 50). Under epidural anaesthesia changes in systolic and diastolic pressure after intravenous infusion were similar in the iloprost and placebo groups.

Table 49. Effect of iloprost on changes in systolic blood pressure after intra-operative intravenous infusion by type of anaesthesia

Type of anaesthesia	Change in pressure (mmHg)	Iloprost n=252			Placebo n=238		
		Number	%	(95%CI)	Number	%	(95%CI)
General	+ >30	8	5	(2-8)	5	4	(2-6)
n=265	+ 11-30	15	10	(6-14)	23	17	(12-22)
	± 0-10	65	44	(38-50)	74	56	(50-62)
	– 11-30	40	27	(21-33)	17	13	(9-17)
	– >30	21	14	(10-18)	14	11	(7-15)
Epidural	+ >30	1	1	(0-2)	1	1	(0-2)
n=193	+ 11-30	12	12	(8-16)	12	12	(8-16)
	± 0-10	56	56	(50-62)	60	61	(55-67)
	– 11-30	24	24	(19-29)	17	17	(12-22)
	– >30	7	7	(4-10)	8	8	(4-12)

Table 50. Effect of iloprost on changes in diastolic blood pressure after intra-operative intravenous infusion by type of anaesthesia

Type of anaesthesia	Change in pressure (mmHg)	Iloprost n=252			Placebo n=238		
		Number	%	(95%CI)	Number	%	(95%CI)
General	+ >30	0	0		2	2	(0-3)
n=265	+ 11-30	15	11	(7-15)	15	12	(8-16)
	± 0-10	84	60	(54-66)	100	76	(71-81)
	– 11-30	33	24	(19-29)	12	9	(5-13)
	– >30	7	5	(2-8)	2	2	(0-3)
Epidural	+ >30	0	0		1	1	(0-2)
n=193	+ 11-30	9	9	(5-13)	3	3	(1-5)
	± 0-10	73	73	(68-78)	78	80	(75-85)
	– 11-30	17	17	(12-22)	15	15	(10-20)
	– >30	1	1	(0-2)	1	1	(0-2)

The proportion of patients with decreases in systolic and diastolic blood pressure after intra-operative intragraft injection were greater in the iloprost group both amongst patients operated under general anaesthesia and amongst those under epidural anaesthesia (Table 51 and 52).

Table 51. Effect of iloprost on changes in systolic blood pressure after intra-operative intragraft injection by type of anaesthesia

Type of anaesthesia	Change in pressure (mmHg)	Iloprost n=252			Placebo n=238		
		Number	%	(95%CI)	Number	%	(95%CI)
General	+ >30	0	0		1	1	(0-2)
n=265	+ 11-30	5	4	(2-6)	12	10	(6-14)
	± 0-10	61	44	(38-50)	93	74	(68-80)
	– 11-30	46	33	(27-39)	17	14	(10-18)
	– >30	27	19	(14-24)	3	2	(0-4)
Epidural	+ >30	1	1	(0-2)	0	0	
n=193	+ 11-30	3	3	(1-5)	8	8	(4-12)
	± 0-10	41	43	(37-49)	77	79	(74-84)
	– 11-30	26	27	(21-33)	12	12	(8-16)
	– >30	25	26	(21-31)	0	0	

Table 52. Effect of iloprost on changes in diastolic blood pressure after intra-operative intragraft injection by type of anaesthesia

Type of anaesthesia	Change in pressure (mmHg)	Iloprost n=252			Placebo n=238		
		Number	%	(95%CI)	Number	%	(95%CI)
General	+ >30	0	0		0	0	
n=265	+ 11-30	3	2	(0-4)	3	2	(0-4)
	± 0-10	88	66	(60-72)	114	92	(88-96)
	– 11-30	41	31	(25-37)	7	6	(3-9)
	– >30	1	1	(0-2)	0	0	
Epidural	+ >30	0	0		0	0	
n=193	+ 11-30	1	1	(0-2)	4	4	(1-7)
	± 0-10	71	74	(69-79)	87	90	(86-94)
	– 11-30	24	25	(20-30)	6	6	(3-9)
	– >30	0	0		0	0	

The changes in heart rate after intra-operative intravenous infusions and intragraft injections of iloprost and placebo were not markedly different in patients under general and epidural anaesthesia, although the numbers of patients with clinically significant changes were too few to yield any firm conclusions (Tables 53 and 54).

Table 53. Effect of iloprost on heart rate after intra-operative intravenous infusion by type of anaesthesia

Type of anaesthesia	Change in heart rate (mmHg)	Iloprost n=252 Number	%	(95%CI)	Placebo n=238 Number	%	(95%CI)
General	+ >15	9	6	(2-10)	5	4	(1-7)
	± 0-15	119	80	(73-87)	121	91	(86-96)
	– >15	21	14	(8-20)	7	5	(1-9)
Epidural	+ >15	5	5	(1-9)	3	3	(0-6)
	± 0-15	87	87	(80-95)	93	95	(91-99)
	– >15	8	8	(3-11)	2	2	(0-4)

Table 54. Effect of iloprost on heart rate after intra-operative intragraft injection by type of anaesthesia

Type of anaesthesia	Change in heart rate (mmHg)	Iloprost n=252 Number	%	(95%CI)	Placebo n=238 Number	%	(95%CI)
General	+ >15	2	1	(0-3)	1	1	(0-2)
	± 0-15	135	97	(94-100)	123	98	(96-100)
	– >15	2	1	(0-3)	1	1	(0-2)
Epidural	+ >15	4	4	(0-8)	0	0	
	± 0-15	91	95	(91-99)	97	100	
	– >15	1	1	(0-3)	0	0	

Postoperative adverse events

Hypotension, nausea, headache, flushing and injection site reactions were all significantly more common during post-operative treatment with iloprost than with placebo (Table 55). One hundred and fifty-four iloprost cases (57.7%, 95%CI 51.8-63.6)) compared to 93 placebo cases (37.2%, 95%CI 31.2-43.2)) reported some kind of adverse experience during the three day post-operative treatment period. However, these were not serious enough to result in more iloprost than placebo patients discontinuing infusions (Table 43). The types of events clearly more common in the iloprost group were nausea, headache, flushing and inflammation at the injection site. There was a slightly greater incidence of

tachycardia in the placebo group, 3.2% (95%CI 1.0-5.4) compared to iloprost, 0.7% (95%CI 0-1.7).

Table 55. Adverse events during post-operative treatment

Adverse experience	Iloprost number (%) n = 267	Placebo number (%) n = 250
One or more	154 (57.7)	93 (37.2)
Nausea	68 (25.5)	27 (10.8)
Hypotension	64 (24.0)	41 (16.4)
Headache	44 (16.5)	13 (5.2)
Flushing	36 (13.5)	8 (3.5)
Dizziness	13 (4.9)	7 (2.8)
Injection site inflammation	13 (4.9)	4 (1.6)
Gastrointestinal disorder	10 (3.7)	7 (2.8)
Hypertension	7 (2.6)	9 (3.6)
Haemorrhage	6 (2.2)	2 (0.8)
Atrial fibrillation	5 (1.9)	2 (0.8)
Bradycardia	4 (1.5)	4 (1.6)
Myocardial infarction	4 (1.5)	4 (1.6)
Chest pain / angina pectoris	4 (1.5)	5 (2.0)
Psychosis	4 (1.5)	3 (1.2)
Lung oedema	3 (1.1)	1 (0.4)
Anaemia	2 (0.7)	0 (0.0)
Anuria	2 (0.7)	0 (0.0)
Dyspnoea	2 (0.7)	1 (0.4)
Malaise	2 (0.7)	0 (0.0)
Tachycardia	2 (0.7)	8 (3.2)
Arterial anomaly	1 (0.4)	0 (0.0)
Arrhythmia	1 (0.4)	0 (0.0)
Cerebrovascular accident	1 (0.4)	2 (0.8)
Confusion	1 (0.4)	0 (0.0)
Death	1 (0.4)	1 (0.4)
Fever	1 (0.4)	1 (0.4)
Atrial flutter	1 (0.4)	0 (0.0)
Heart failure	1 (0.4)	1 (0.4)
Hypoventilation	1 (0.4)	0 (0.0)

Hypovolaemia	1	(0.4)	0	(0.0)
Oliguria	1	(0.4)	0	(0.0)
Pain	1	(0.4)	1	(0.4)
Somnolence	1	(0.4)	0	(0.0)
Increased sweating	1	(0.4)	2	(0.8)
Apnoea	0	(0.0)	1	(0.4)
Cardiovascular disorder	0	(0.0)	1	(0.4)
Dry mouth	0	(0.0)	1	(0.4)
Pulmonary embolus	0	(0.0)	1	(0.4)
Ventricular extrasystoles	0	(0.0)	1	(0.4)
Eye disorder	0	(0.0)	1	(0.4)
Haematuria	0	(0.0)	1	(0.4)
Cerebral ischaemia	0	(0.0)	1	(0.4)
Abnormal liver function test	0	(0.0)	1	(0.4)
Pruritis	0	(0.0)	1	(0.4)
Peripheral vascular disorder	0	(0.0)	1	(0.4)
Vertigo	0	(0.0)	1	(0.4)

Division of the incidence of haemorrhage between those patients who were receiving oral anticoagulants and those who were not revealed that all eight cases of haemorrhage recorded as adverse events were in patients not receiving oral anticoagulants. The division between iloprost and placebo is shown above (Table 55). The incidences of cardiovascular events with a possible thrombotic aetiology during the three-day post-operative study treatment period did not differ significantly with iloprost irrespective of the use of oral anticoagulants (Table 56).

Table 56. Major cardiovascular events by use of oral anticoagulant

	Number of patients (%)					
Oral anticoagulants	Yes		No		Yes	No
Iloprost	Yes n=55	No n=49	Yes n=211	No n=200	n=104	n=411
Myocardial infarction	4 (7.3)	1 (2.0)	4 (1.9)	3 (1.5)	5 (4.8)	7 (1.7)
Angina / chest pain	4 (7.3)	2 (4.1)	4 (1.9)	3 (1.5)	6 (5.8)	7 (1.7)
Cerebrovascular event	1 (1.8)	1 (2.0)	1 (0.5)	1 (0.5)	2 (1.9)	2 (0.5)
Pulmonary embolus	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.2)

In both treatment groups there was an expected large proportion of patients exhibiting an increase in blood pressure during the first postoperative infusion of study medication (Table 57). There was no evidence of a larger number of patients with hypotension in the iloprost group, in agreement with the judgement of the clinician (Table 55), but diastolic pressure measurements showed evidence of less patients exhibiting an increase in blood pressure during the course of the infusions on the first and second day (Table 58). Measurements of heart rate indicate that changes with postoperative treatment did not differ between the two treatment groups except on day 3 when a greater number of patients receiving iloprost exhibited a rise in heart rate of >15 beats/min during the infusion (Tables 59).

Table 57. Maximum changes in systolic blood pressure during postoperative intravenous infusions of study medication

Time point	Change in pressure (mmHg)	Iloprost n=252		Placebo n=238	
		Number	% (95%CI)	Number	% (95%CI)
Day 1	+ >30	59	23 (18-28)	65	27 (21-33)
	+ 11-30	83	33 (27-36)	75	32 (26-38)
	± 0-10	90	35 (29-41)	75	32 (26-38)
	– 11-30	17	7 (4-10)	17	7 (4-10)
	– >30	5	2 (0-4)	5	2 (0-4)
Day 2	+ >30	21	9 (5-13)	28	12 (8-16)
	+ 11-30	79	33 (27-36)	89	39 (33-45)
	± 0-10	122	51 (45-57)	94	42 (36-48)
	– 11-30	16	7 (4-10)	11	5 (2-8)
	– >30	3	1 (0-2)	5	2 (0-4)
Day 3	+ >30	24	11 (7-15)	24	11 (7-15)
	+ 11-30	73	32 (26-38)	70	33 (27-39)
	± 0-10	121	53 (47-59)	107	51 (45-57)
	– 11-30	10	4 (2-7)	10	5 (2-8)
	– >30	0	0	1	1 (0-1)

Table 58. Maximum changes in diastolic blood pressure during postoperative intravenous infusions of study medication

Time point	Change in pressure (mmHg)	Iloprost n=252 Number	% (95%CI)	Placebo n=238 Number	% (95%CI)
Day 1	+ >30	18	8 (5-11)	14	6 (3-9)
	+ 11-30	75	31 (25-37)	94	42 (36-48)
	± 0-10	135	57 (51-63)	105	47 (41-53)
	– 11-30	11	5 (2-7)	13	6 (3-9)
	– >30	0	0	0	0
Day 2	+ >30	1	0 (0-1)	9	4 (2-7)
	+ 11-30	59	26 (21-31)	60	28 (22-34)
	± 0-10	162	71 (65-77)	141	65 (59-71)
	– 11-30	6	3 (1-5)	5	2 (0-4)
	– >30	0	0	2	1 (0-2)
Day 3	+ >30	5	2 (0-4)	4	2 (0-4)
	+ 11-30	51	24 (19-29)	49	24 (19-29)
	± 0-10	160	74 (69-79)	150	74 (68-80)
	– 11-30	0	0	0	0
	– >30	0	0	0	0

Table 59. Maximum changes in heart rate during postoperative infusions of study medication

Time point	Change in heart rate (mmHg)	Iloprost n=252 Number	% (95%CI)	Placebo n=238 Number	% (95%CI)
Day 1	+ >15	92	36 (30-42)	80	34 (28-40)
	± 0-15	157	62 (56-68)	144	61 (65-67)
	– >15	5	2 (0-4)	12	5 (2-8)
Day 2	+ >15	65	27 (21-33)	48	21 (16-26)
	± 0-15	172	71 (65-77)	173	77 (71-82)
	– >15	4	2 (0-3)	5	2 (0-4)
Day 3	+ >15	55	24 (19-29)	31	3 (0-6)
	± 0-15	171	75 (70-80)	178	95 (91-99)
	– >15	2	1 (0-2)	1	2 (0-4)

Postoperative adverse events after the treatment period

During the first 14 days post-operatively (up to discharge from hospital) the incidences of all adverse events and most importantly major cardiovascular events such as myocardial infarction, cerebrovascular accident and death from any cause did not differ greatly in the two treatment groups (Table 60). The incidences for iloprost and placebo respectively for the most important events were: myocardial infarction 7 (3%, 95%CI 1-5) and 10 (4%, 95%CI 2-7), cerebrovascular accident 3 (1%, 95%CI 0-2) and 2 (1%, 95%CI 0-2), death from any cause 8 (3%, 95%CI 1-5) and 5 (2%, 95%CI 0-4).

Table 60. Post-operative adverse medical events from the end of the treatment period up to 14 days (or discharge). All events occurring in more than one patient.

Adverse experience	Iloprost number (%) n = 267	Placebo number (%) n = 250
One or more	51 (19.5)	52 (21.2)
Death	8 (3.1)	5 (2.0)
Myocardial infarction	7 (2.7)	10 (4.1)
Cerebrovascular accident	3 (1.1)	2 (0.8)
Lung oedema	3 (1.1)	0 (0.0)
Cardiac arrest	3 (1.1)	0 (0.0)
Pulmonary embolus	2 (0.8)	0 (0.0)
Heart failure	2 (0.8)	1 (0.4)
Hypotension	2 (0.8)	1 (0.4)
Infection	2 (0.8)	3 (1.2)
Oliguria	2 (0.8)	0 (0.0)
Chest pain / angina pectoris	3 (1.2)	3 (1.2)
Sepsis	2 (0.8)	0 (0.0)
Shock	2 (0.8)	1 (0.4)
Abscess	1 (0.4)	1 (0.4)
Arterial anomaly	1 (0.4)	1 (0.4)
Apnoea	1 (0.4)	1 (0.4)
Dyspnoea	1 (0.4)	2 (0.8)
Atrial fibrillation	1 (0.4)	3 (1.2)
Necrosis	1 (0.4)	1 (0.4)

The incidence of major cardiovascular events and death from all causes did not differ between the two treatment groups (Table 61) over the whole 12 month study period.

Death occurred in 19.0% of patients and the most common cardiovascular event, other than graft occlusion or surgical intervention for PAOD, was myocardial infarction in 8.3% of cases.

Table 61. Selected major cardiovascular adverse events from beginning of surgery to the end of 12 months follow-up (number of patients experiencing an event)

Adverse experience	Iloprost number (%) n = 267		Placebo number (%) n = 250		Total number (%) n = 517	
Death	53	(19.9)	45	(18.0)	98	(19.0)
Myocardial infarction	23	(8.6)	20	(8.0)	43	(8.3)
Cerebrovascular accident	9	(3.4)	3	(1.2)	12	(2.3)
Heart failure/left ventricular failure	11	(4.1)	7	(2.8)	18	(3.5)
Thrombosis	3	(1.1)	2	(0.8)	5	(1.0)
Haemorrhage	10	(3.7)	5	(2.0)	15	(2.9)
Pulmonary embolus	3	(1.1)	3	(1.2)	6	(1.2)
Cardiac arrest	3	(1.1)	1	(0.4)	4	(0.8)

4.4. Postoperative management

Heparin was administered to the majority of patients in both treatment groups intra-operatively at doses of ≤5000 international units (Table 62). Post-operatively only a minority of patients in each group received intravenous heparin, usually at a daily dose of 5,000 or 10,000 international units. There were no great differences between the treatment groups in terms of number of patients receiving heparin or the doses most commonly administered.

Table 62. Administration of heparin intra-operatively and postoperatively

Time point	Heparin dose	Iloprost n=267 number (%)	Placebo n=250 number (%)	Total n=517 number (%)
Operation	0 U	92 (34.5)	84 (33.6)	176 (34.0)
	1 - 5000 U	169 (63.3)	150 (60.0)	319 (61.7)
	5001 - 7500 U	3 (1.1)	9 (3.6)	12 (2.3)
	7501 - 15000 U	2 (0.7)	4 (1.6)	6 (1.2)
	15001- 40000 U	1 (0.4)	3 (1.2)	4 (0.8)
Day 1 post-op	0 U	157 (58.8)	139 (55.6)	296 (57.3)
	1 - 5000 U	41 (15.4)	32 (12.8)	73 (14.1)
	5001 - 7500 U	1 (0.4)	2 (0.8)	3 (0.6)
	7501 - 15000 U	51 (19.1)	54 (21.6)	105 (20.3)
	15001- 40000 U	17 (6.4)	23 (9.2)	40 (7.7)
Day 2 post-op	0 U	155 (58.1)	139 (55.6)	294 (56.9)
	1 - 5000 U	26 (9.4)	26 (10.4)	52 (10.1)
	5001 - 7500 U	2 (0.7)	0 (0.0)	2 (0.4)
	7501 - 15000 U	67 (25.1)	63 (25.2)	130 (25.1)
	15001- 40000 U	17 (6.4)	22 (8.8)	39 (7.5)
Day 3 post-op	0 U	152 (56.9)	139 (55.6)	291 (56.3)
	1 - 5000 U	22 (8.2)	23 (9.2)	45 (8.7)
	5001 - 7500 U	2 (0.7)	0 (0.0)	2 (0.4)
	7501 - 15000 U	70 (26.2)	67 (26.8)	137 (26.5)
	15001- 40000 U	21 (7.9)	21 (8.4)	42 (8.1)

The number of patients using other antithrombotic agents during the follow-up period was not very different in the iloprost and placebo groups, although the proportion of patients taking aspirin was marginally higher in the placebo group, 31% (95%CI 25-36), compared to the iloprost group, 25% (95%CI 20-30) (Table 63).

Table 63. Postoperative antithrombotic medication other than heparin. Numbers represent the patients taking the medication at any of the postoperative assessments.

Agent	Iloprost n=267 number (%)	Placebo n=250 number (%)	Total n=517 number (%)
Any anticoagulant	98 (36.7)	92 (36.8)	190 (36.8)
Warfarin	50 (18.7)	51 (20.4)	101 (19.5)
Marcoumar	10 (3.7)	8 (3.2)	18 (3.5)
Acenocoumarol	37 (13.9)	33 (13.2)	70 (13.5)
Dicoumarol	1 (0.4)	0 (0.0)	1 (0.2)
Any platelet inhibitor	68 (25.5)	78 (31.2)	146 (28.2)
Aspirin	67 (25.1)	77 (30.8)	144 (27.9)
Dipyridamole	1 (0.4)	0 (0.0)	1 (0.2)
Other	1 (0.4)	1 (0.4)	2 (0.4)

Wound infections in the early postoperative period were reported in less than 15% of patients overall and in similar numbers in the two treatment groups (Table 64).

Table 64. Wound infections in the early postoperative period

Time point	Depth	Iloprost number (%)	Placebo number (%)	Total number (%)
Day 3	None	251 (94.0)	240 (96.0)	491 (95.0)
	Superficial	15 (5.6)	9 (3.6)	24 (4.6)
	Deep	1 (0.4)	1 (0.4)	2 (0.4)
Discharge	None	228 (85.4)	217 (86.8)	445 (86.1)
	Superficial	35 (13.1)	25 (10.0)	60 (11.6)
	Deep	4 (1.5)	8 (3.2)	12 (2.3)

Post-operative graft surveillance with duplex ultrasound was performed by 17 of the 21 centres participating in the trial on 272 (52.6%) of the patients in total. Of those patients

undergoing surveillance, 78 (28.7%) were found to have haemodynamically significant stenoses. Nineteen patients (7.0%) of those patients successfully underwent dilatation by percutaneous transluminal angioplasty (PTA) (Table 65).

Table 65. Results of vein graft surveillance with duplex ultrasound

	Iloprost n = 137	Placebo n = 135	Total n = 272
Haemodynamically significant stenosis			
no. patients	47 (34.3%)	31 (23.0%)	78 (28.7%)
no. stenoses	59	39	98
Stenosis dilatations			
no. patients	15 (5.7%)	4 (1.4%)	19 (3.5%)

The largest number of stenoses, 54 (43.5%), were found at the distal anastomosis. Smaller numbers were found at the proximal anastomosis, 37 (29.8%), and in the mid portion of the graft, 32 (25.8%). The location of one stenosis was not specified by the surgeon. The majority of grafts scanned were vein grafts and there was some evidence of differences in stenosis rates between the different materials (Table 66).

Table 66. Number of patients with different graft materials undergoing graft surveillance and frequency of stenoses

	Number of grafts		
Graft material	Performed	Scanned (% of grafts performed)	Stenosed (% of those scanned)
In situ saphenous vein	292	197 (67)	49 (25)
Reversed saphenous vein	90	50 (56)	12 (24)
Composite vein-vein	42	30 (71)	13 (43)
Composite prosthetic-vein	29	12 (41)	2 (17)
Prosthetic	63	32 (51)	3 (9)
Not classified	1	1 (100)	1 (100)
All grafts containing vein	453	289 (64)	76 (26)
Total	517	322 (62)	80 (25)

Eighty-one percent of male patients and 75% of female patients were eligible for graft surveillance. Of the eligible patients, rather more of the males were included in the surveillance programme than the females. Amongst the patients with grafts consisting of, or containing, vein segments, stenoses were detected more frequently in females (35%) than in males (22%) (Table 67). The greater frequency of stenoses in female patients was most notable in *in situ* and reversed vein grafts (Table 67).

Table 67. Frequency of graft stenoses by gender and graft material

		Grafts with stenoses (%)			
Graft material	Scanned grafts	Males n=209		Females n=112	
In situ saphenous vein	197	28 / 135	(21)	21 / 62	(34)
Reversed saphenous vein	50	6 / 38	(16)	6 / 12	(50)
Composite vein-vein	30	7 / 17	(41)	6 / 13	(46)
Composite prosthetic-vein	12	1 / 3	(33)	1 / 9	(11)
Prosthetic	32	2 / 16	(13)	1 / 16	(6)
All grafts containing vein	289	42 / 193	(22)	34 / 96	(35)
Total	321	44 / 209	(21)	35 / 112	(31)

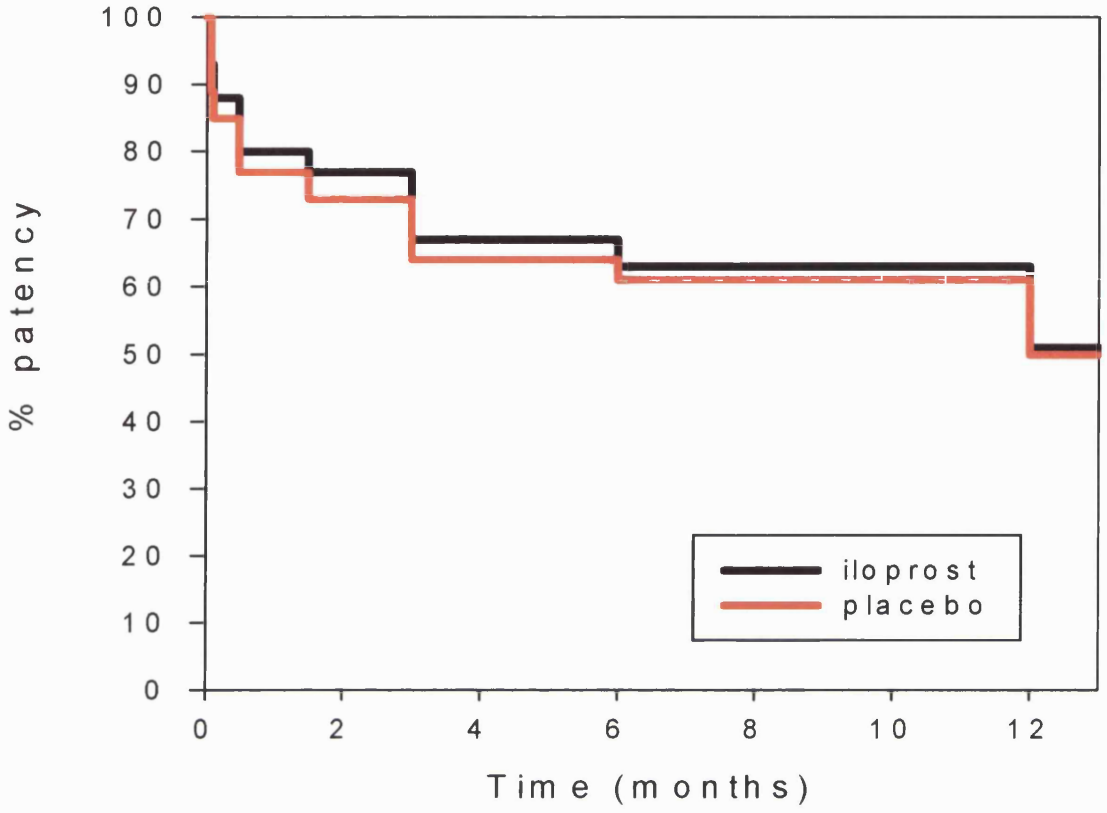
4.5. Efficacy

Graft patency

The first analyses of graft patency presented are the overall patencies in the two treatment groups although these were not the primary analysis of interest. This is followed by analysis of the graft patencies by graft material and then the primary efficacy analysis, which was the comparison of primary graft patency in the patients receiving vein grafts. Finally, the analysis of graft patency in the smaller group of patients receiving prosthetic grafts is presented.

Overall patencies by life-table analysis showed little difference between the two treatment groups when all patients are included irrespective of graft material (Figures 16-18), although patencies in the iloprost treated group were at most time points numerically higher in each category of patency. Primary patency at the end of the 12 month follow-up period in evaluable patients was 51.3% in the iloprost group (95%CI 44.8-57.8) and 52.6% in the placebo group (95%CI 45.9-59.3). Assisted primary patency after 12 months was 57.1% for iloprost (95%CI 50.6-63.6) and 55.9% for placebo (95%CI 49.2-62.6). Secondary patency after 12 months was 62.8% for iloprost (95%CI 46.2-69.4) compared to 60.2% for placebo (95%CI 53.6-66.8).

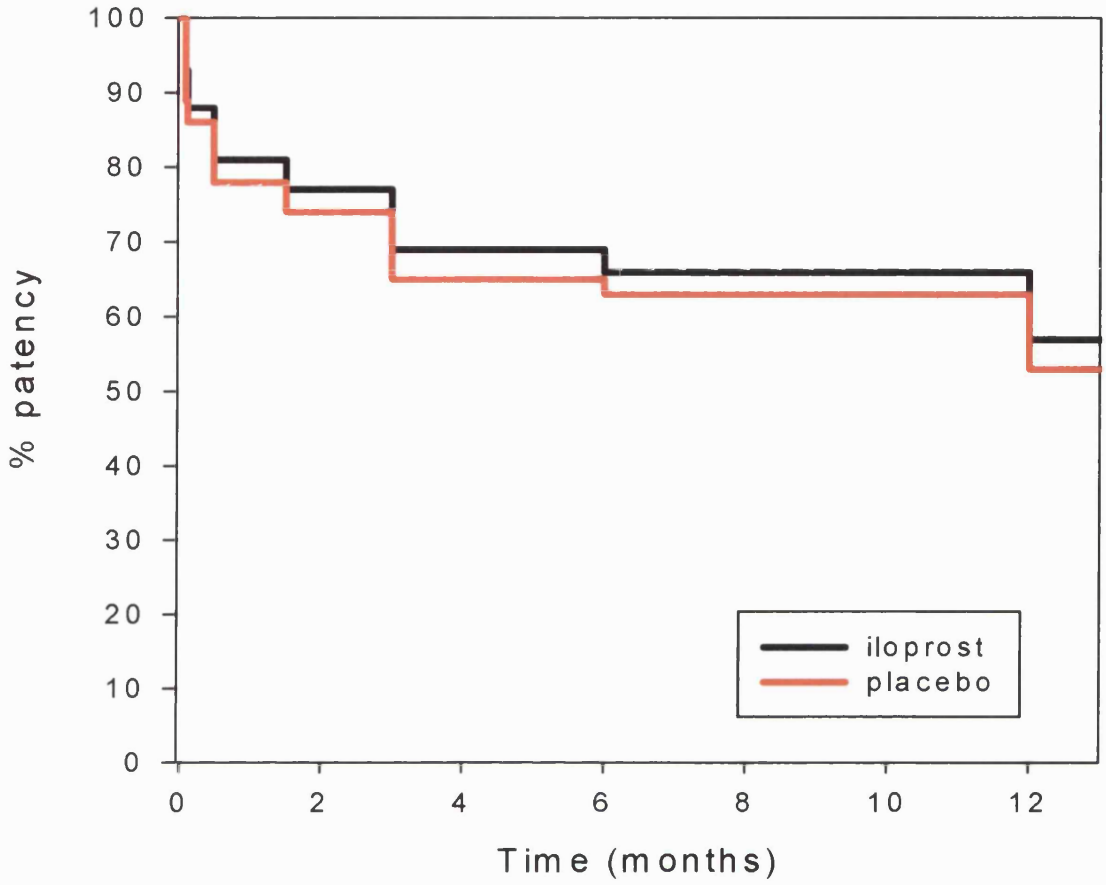
Figure 16. Primary patency in all grafts by study treatment irrespective of graft material



Patients at risk:

Time (months)	*0.07*	*0.10*	*0.47*	*1.50*	*3.00*	*6.00*	*12.00*
Iloprost	251	233	216	194	185	154	142
Placebo	237	210	199	178	168	139	132

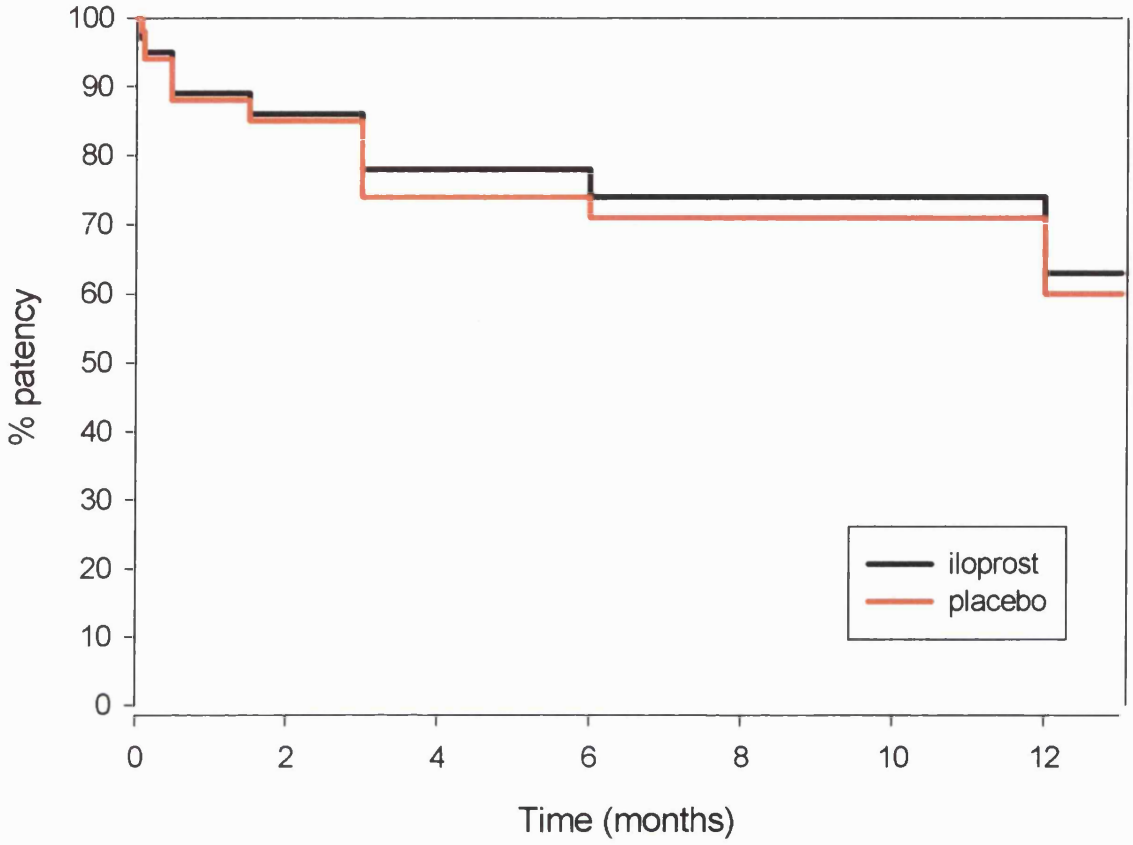
Figure 17. Assisted primary patency in all grafts by study treatment irrespective of graft material.



Patients at risk:

Time (months)	*0.07*	*0.10*	*0.47*	*1.50*	*3.00*	*6.00*	*12.00*
Iloprost	250	232	215	2195	186	158	147
Placebo	235	209	198	179	169	141	136

Figure 18. Secondary patency in all grafts by study treatment irrespective of graft material.



Patients at risk:

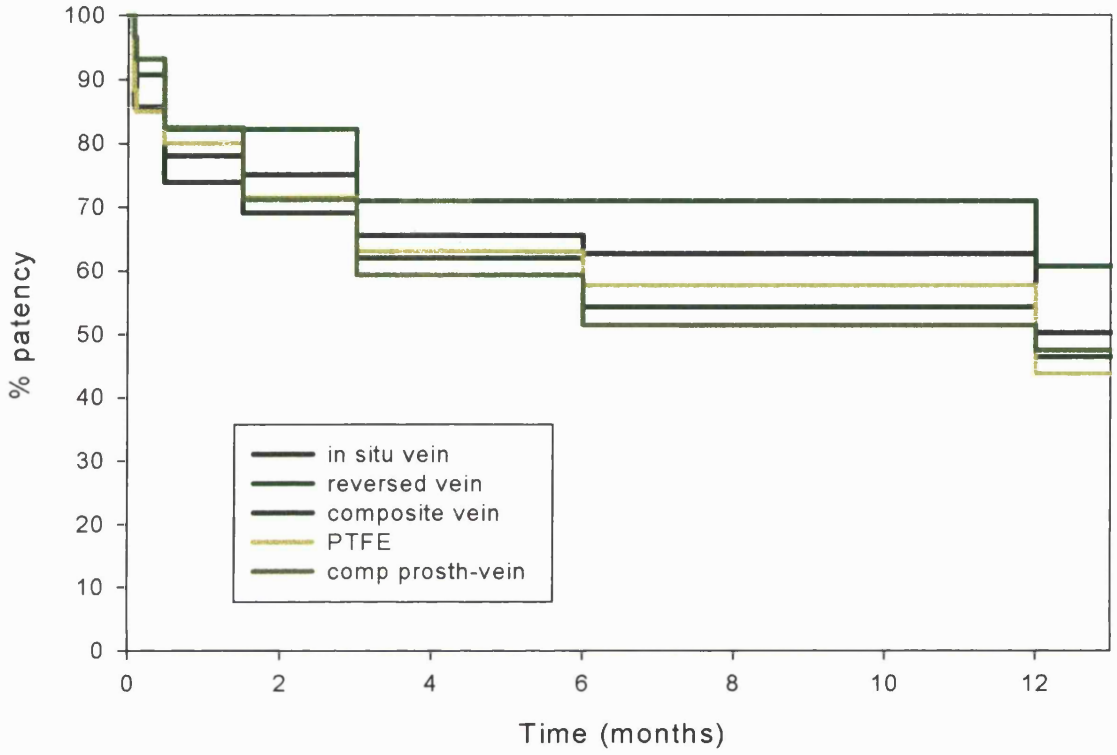
Time (months)	*0.07*	*0.10*	*0.47*	*1.50*	*3.00*	*6.00*	*12.00*
Iloprost	247	240	231	212	204	174	162
Placebo	232	227	215	194	186	153	147

Patency with different graft materials

The possibility of different results in patients with different graft materials was confirmed when bypass patency was compared for each type of graft material (Figure 19). The best results were obtained in patients who received reversed vein bypass grafts while composite vein grafts did not appear to offer any advantage over prosthetic grafts.

Comparison of primary patency in all vein grafts with all prosthetic and vein-prosthetic composite grafts in Kaplan-Meier analyses appeared to confirm the superiority of vein grafts (Figures 20 and 21).

Figure 19. Primary patency by graft material and surgical procedure

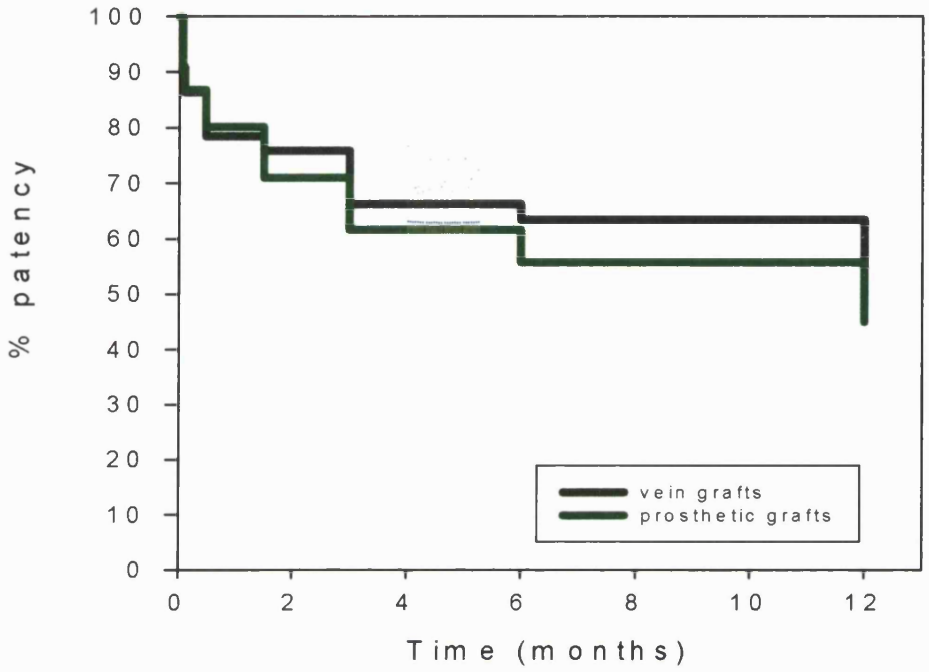


Patients at risk:

Graft material	*0.07*	*0.10*	*0.47*	*1.50*	*3.00*	*6.00*	*12.00*
in situ vein	269	245	227	205	197	162	151
reversed vein	86	80	74	66	66	55	55
composite vein	42	36	36	31	29	24	21
PTFE	60	53	51	47	42	36	33
composite prosthetic-vein	29	28	26	22	18	15	13

Primary patency of vein grafts in all evaluable patients at 12 months was 50.4% (95%CI 45.3-55.5) and for all prosthetic grafts 44.2% (95%CI 33.7-54.7).

Figure 20. Primary patency compared in vein and prosthetic grafts

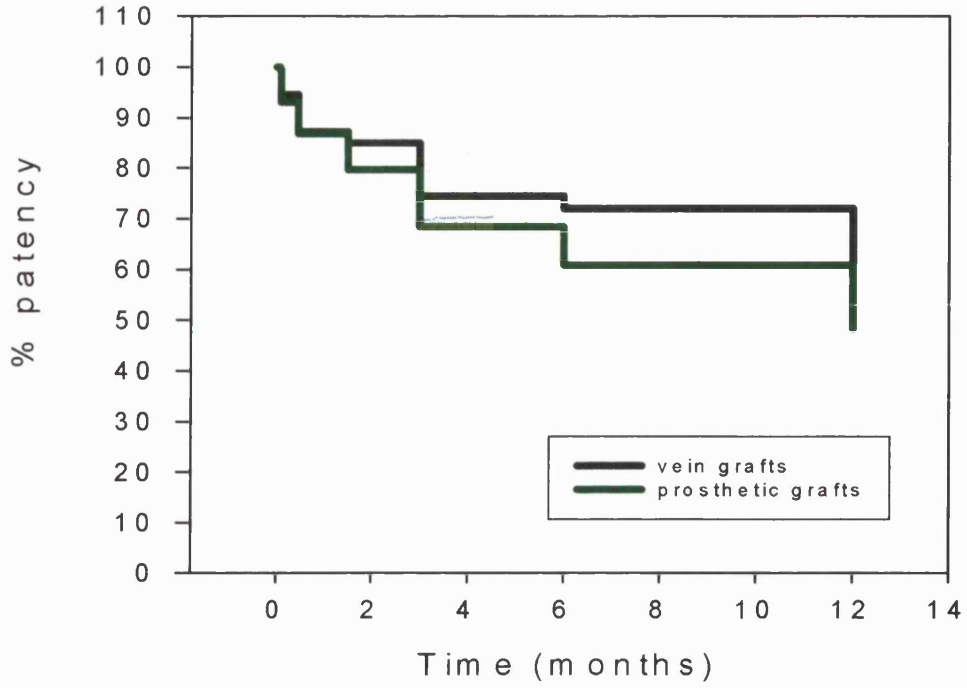


Patients at risk:

Time (months)	*0.07*	*0.10*	*0.47*	*1.50*	*3.00*	*6.00*	*12.00*
Vein grafts	397	361	337	302	292	241	227
Prosthetic grafts	91	82	78	70	61	52	47

The secondary patency of vein grafts in all evaluable patients at 12 months was 59.4% (95%CI 54.0-64.8) compared to a secondary patency in prosthetic grafts at 12 months of 47.5% (95%CI 36.6-58.4).

Figure 21. Secondary patency compared in vein and prosthetic grafts



Patients at risk:

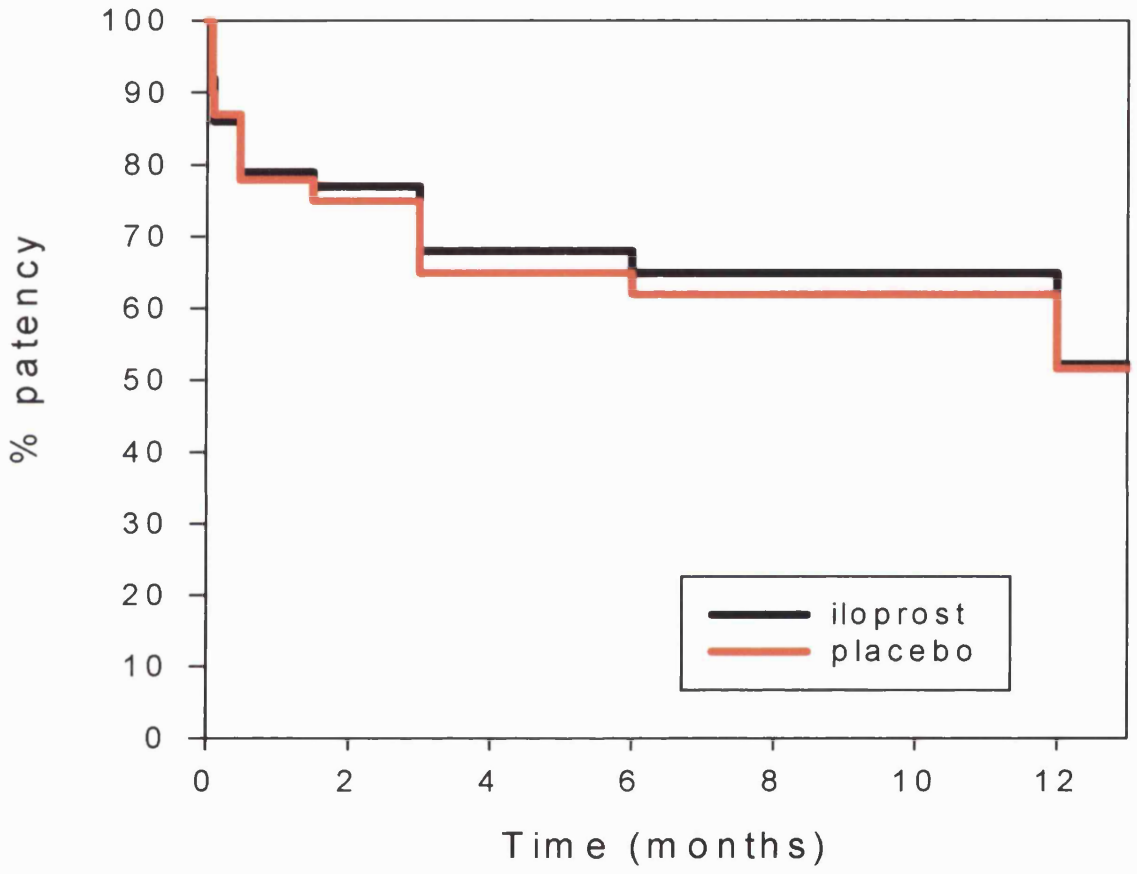
Time (months)	*0.07*	*0.10*	*0.47*	*1.50*	*3.00*	*6.00*	*12.00*
Vein grafts	349	339	324	293	284	234	222
Prosthetic grafts	85	83	78	71	64	54	48

Vein graft patency

Life-table analysis of patencies in vein grafts, as in the analysis of grafts of all materials, did not show any large differences between the treatment groups, although once again patencies in the iloprost treated group were generally higher for each category of patency (Figures 22-24). The primary patency rates in the two treatment groups were not significantly different (p=0.81). Primary patency at the end of the 12 month follow-up period in evaluable patients was 52.6% in the iloprost group (95%CI 45.2-60.0) and 54.2% in the placebo group (95%CI 46.9-61.5). The difference of 1.6% in primary patency rates between the treatment groups at 12 months had a 95% confidence interval

ranging from 12.0% in favour of placebo to 8.8% in favour of iloprost. Assisted primary patency after 12 months in evaluable patients was 60.0% for iloprost (95%CI 52.7-67.3) and 58.1% for placebo (95%CI 50.9-65.3). Secondary patency after 12 months was 65.7% with iloprost (95%CI 58.7-72.7) compared to 62.0% for placebo (95%CI 54.9-69.1).

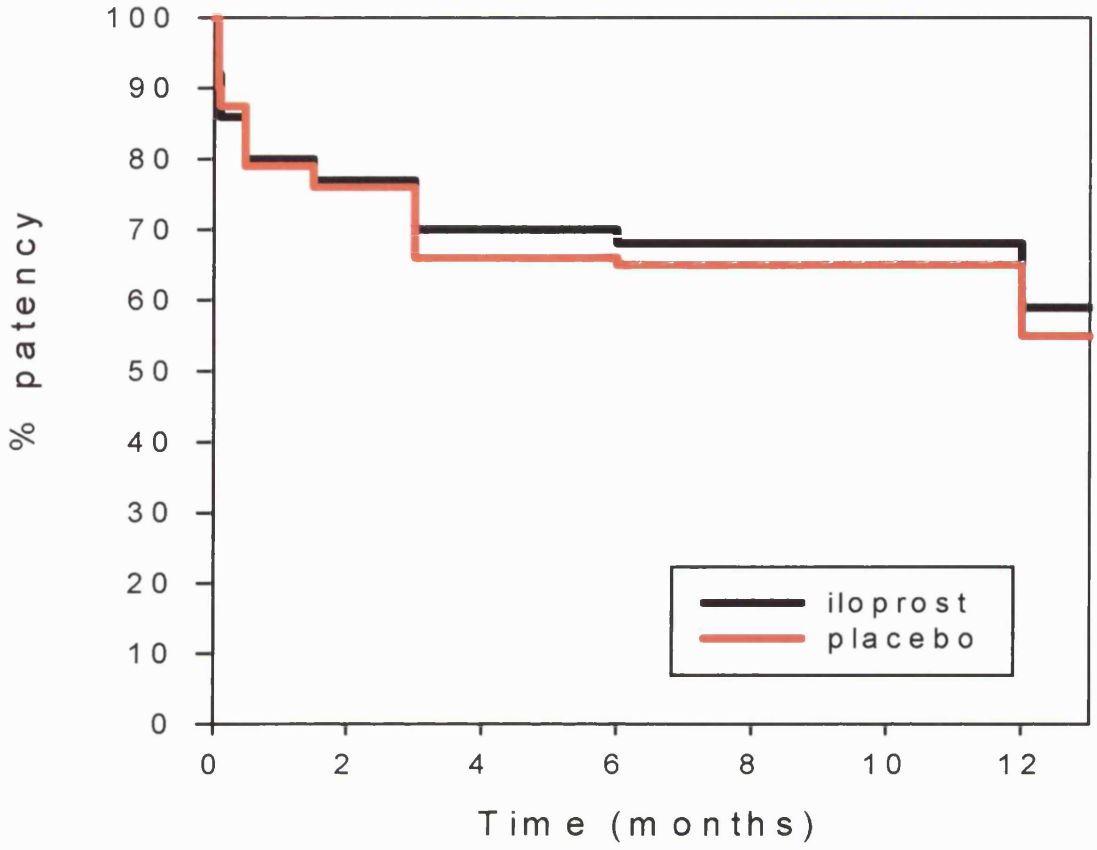
Figure 22. Primary patency assessments in vein grafts by study treatment



Patients at risk:

Time (months)	*0.07*	*0.10*	*0.47*	*1.50*	*3.00*	*6.00*	*12.00*
Iloprost	195	180	164	150	145	121	113
Placebo	202	181	173	152	147	120	114

Figure 23. Assisted primary patency assessments in vein grafts by study treatment

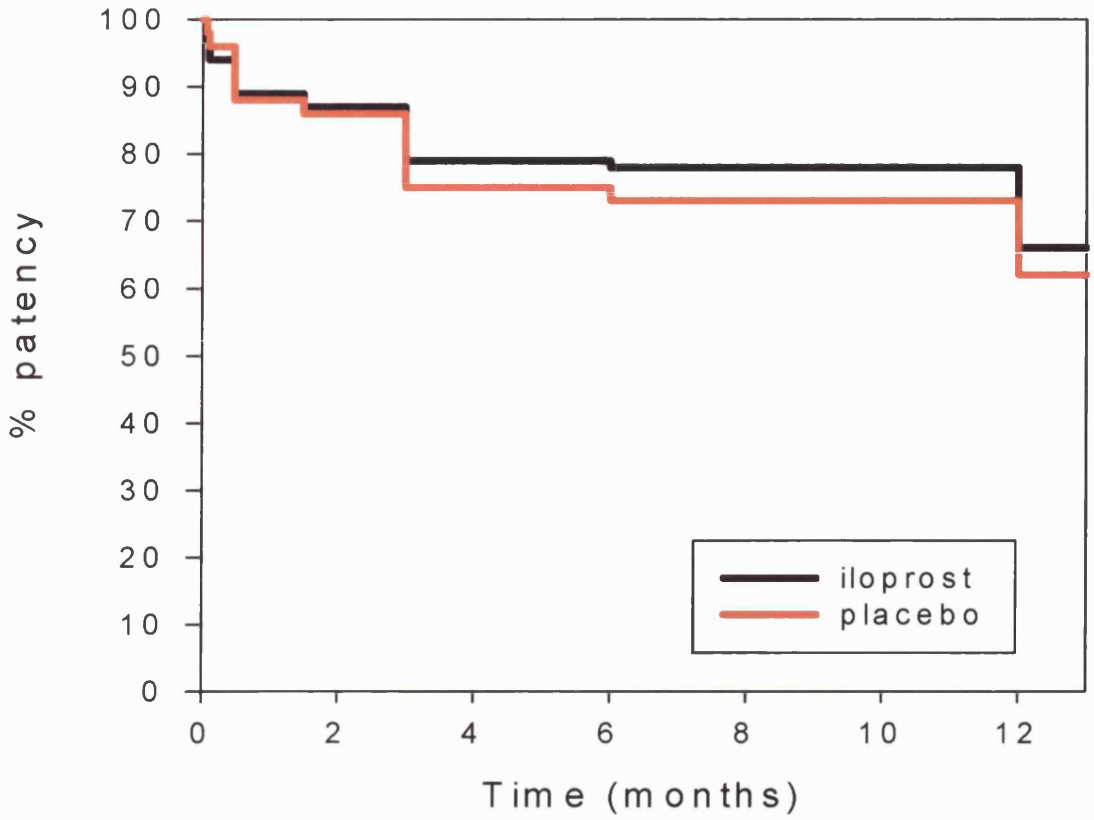


Patients at risk:

Time (months)	*0.07*	*0.10*	*0.47*	*1.50*	*3.00*	*6.00*	*12.00*
Iloprost	194	179	163	150	145	125	118
Placebo	200	180	172	153	148	122	118

The time course of graft failures showed that 22% of vein grafts had suffered an occlusion by the time of discharge, almost half of those occluding in the first 12 months. Secondary patency, however, was still 87% overall at discharge, the majority of permanent occlusions occurring after discharge.

Figure 24. Secondary patency assessments in vein grafts by study treatment



Patients at risk:

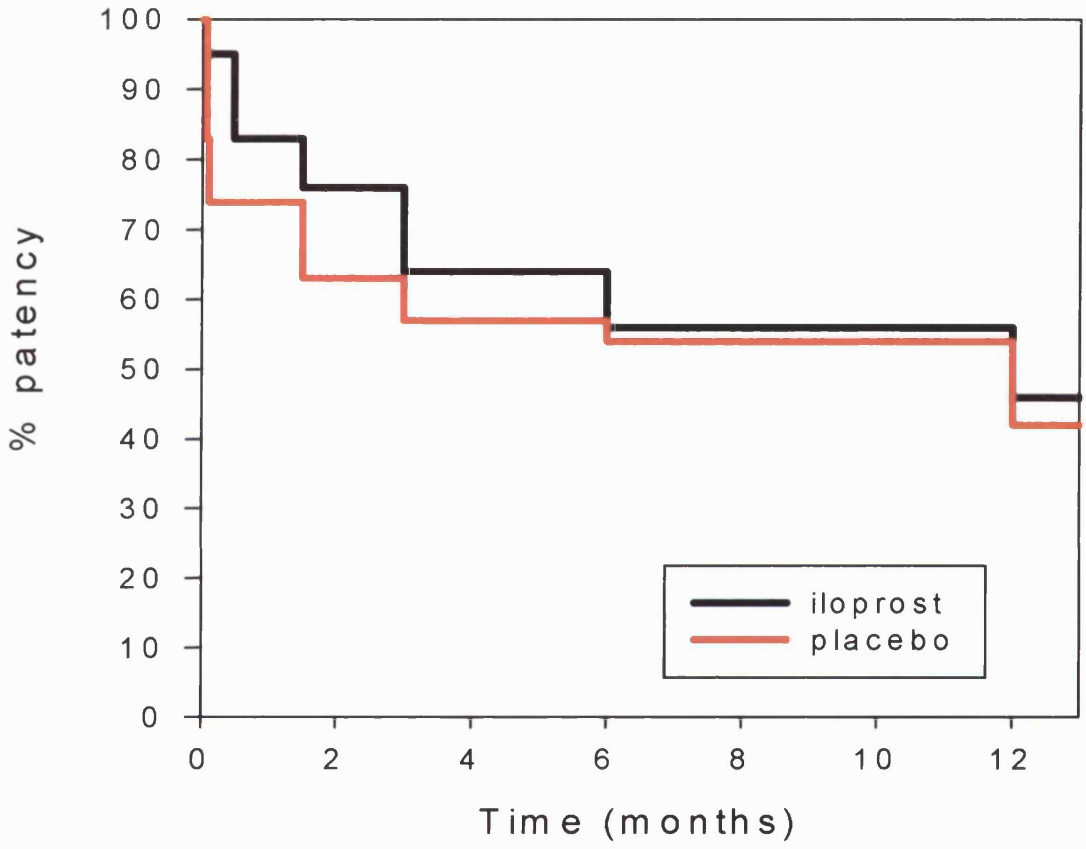
Time (months)	*0.07*	*0.10*	*0.47*	*1.50*	*3.00*	*6.00*	*12.00*
Iloprost	191	185	177	165	160	138	131
Placebo	198	194	186	165	161	131	126

Prosthetic graft patency

Life-table analysis of patencies in prosthetic grafts, as in the analysis of grafts of all materials and vein grafts alone, did not show any large differences between the treatment groups at the end of the follow-up period (Figures 25 and 26). Primary patency at the end of the 12 month follow-up period was 46.0% in the iloprost group (95%CI 32.2-59.8) and 43.8% in the placebo group (95%CI 26.6-61.0). However, there was a maximum difference of 20.4% in favour of the iloprost group between the

treatment groups at 3 days, the end of the treatment period, with a confidence interval ranging from 4.2% to 36.0% in favour of iloprost. Assisted primary patency results in prosthetic grafts were identical to primary patency. Secondary patency of evaluable patients after 12 months was 52.0% with iloprost (95%CI 38.2-65.8) compared to 50.0% for placebo (95%CI 32.7-67.3).

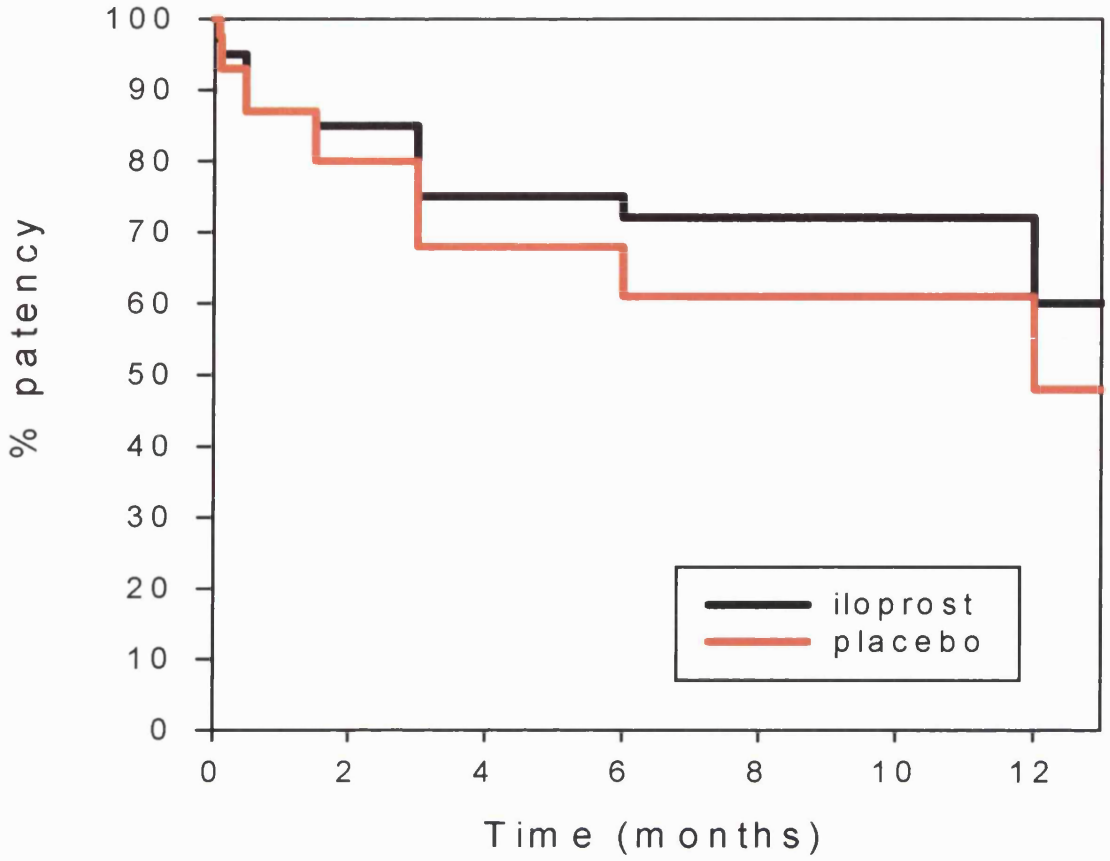
Figure 25. Primary patency assessments in prosthetic grafts by study treatment



Patients at risk:

Time (months)	*0.07*	*0.10*	*0.47*	*1.50*	*3.00*	*6.00*	*12.00*
Iloprost	55	52	51	43	39	32	28
Placebo	35	29	29	26	21	19	18

Figure 26. Secondary patency assessments in prosthetic grafts by study treatment



Patients at risk:

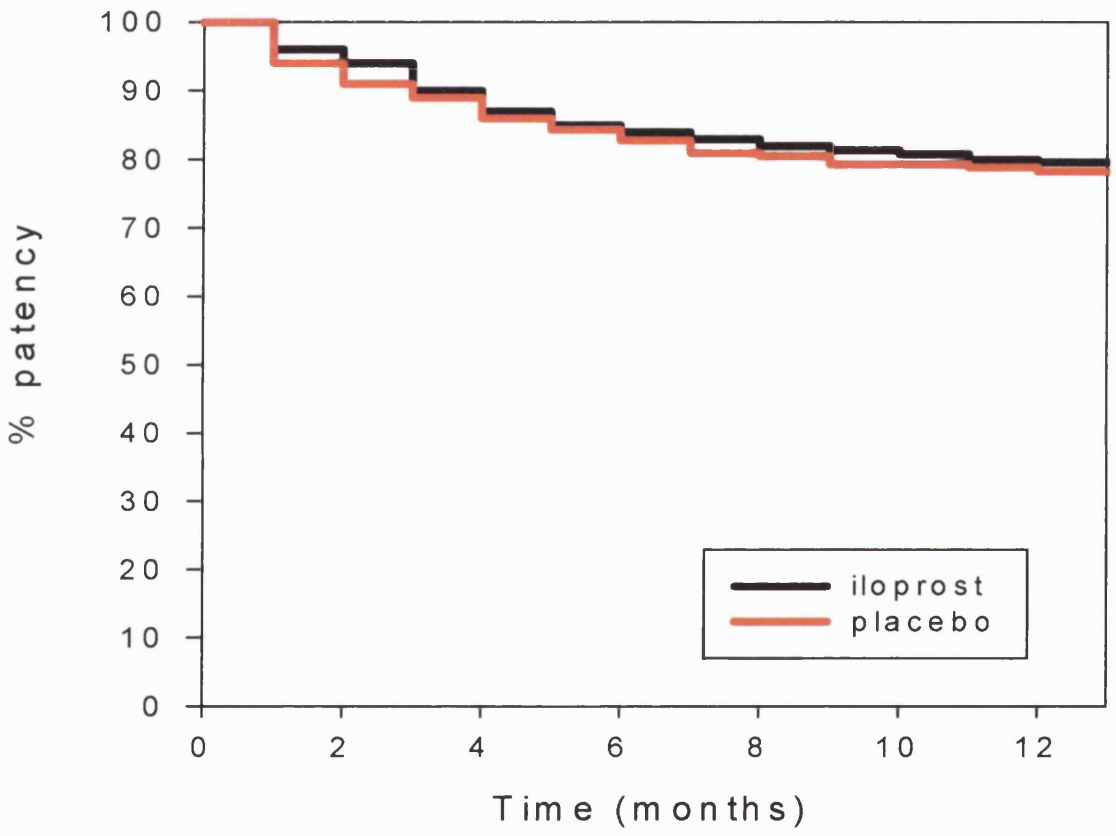
Time (months)	*0.07*	*0.10*	*0.47*	*1.50*	*3.00*	*6.00*	*12.00*
Iloprost	55	51	50	42	38	30	28
Placebo	35	31	30	29	24	22	21

The majority of graft occlusions in the placebo group occurred before discharge, whereas those in the iloprost group occurred mostly after discharge. Loss of secondary patency in prosthetic grafts occurred most commonly after 6 weeks in both treatment groups.

Limb survival and amputations

Life-table analysis yielded similar limb survival curves in the two treatment groups for both vein grafts (Figure 27) and prosthetic grafts (Figure 28). At the end of the 12 month follow-up the limb survival rates for iloprost and placebo respectively were 75.9% (95%CI 69.2-82.6) and 76.0% (95%CI 69.7-82.3) for vein grafts and 68.8% (95%CI 55.7-81.9) and 67.7% (95%CI 52.2-82.2) for prosthetic grafts. The overall limb survival figures for the different materials were 76.0% for vein grafts and 68.4% for prosthetic grafts.

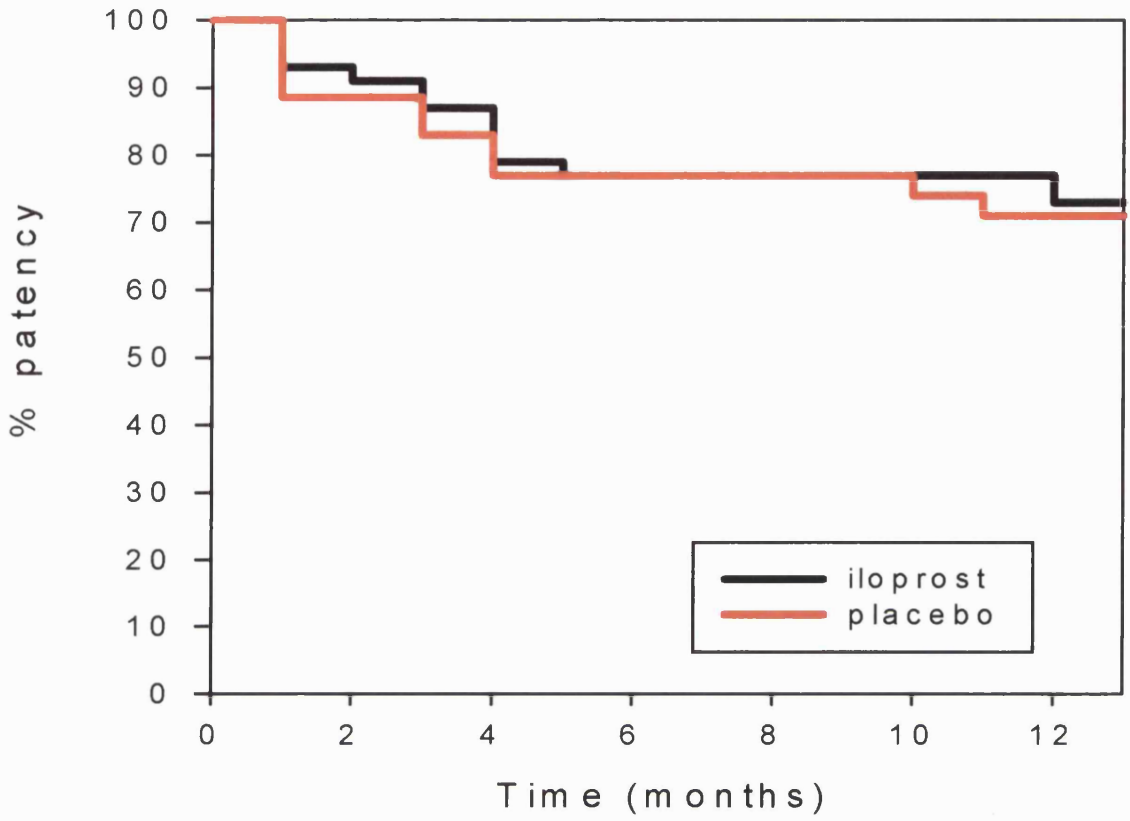
Figure 27. Limb survival in vein grafts by study treatment



Patients at risk:

Time (months)	*1*	*2*	*3*	*4*	*6*	*9*	*12*
Iloprost	206	183	176	166	153	138	121
Placebo	211	186	178	170	153	141	134

Figure 28. Limb survival in prosthetic grafts by study treatment



Patients at risk:

Time (months)	*1*	*2*	*3*	*4*	*6*	*9*	*12*
Iloprost	56	49	47	45	40	38	35
Placebo	35	35	31	29	26	26	21

Minor amputations, toes or forefoot amputations, occurred in equal numbers in the two treatment groups (Table 68). Over 80% (41/49) of the minor amputations were performed within two months of the bypass surgery and most of these were performed within one month of bypass.

Table 68. Cumulative minor amputations by month and treatment group

Month	Number of patients (%)					
	Iloprost (n=267)		Placebo (n=250)		Total (n=517)	
1	16	(6.0)	19	(7.6)	35	(6.8)
2	19	(7.1)	21	(8.4)	40	(7.7)
3	21	(7.9)	22	(8.8)	43	(8.3)
4	22	(8.2)	22	(8.8)	44	(8.5)
5	23	(8.6)	22	(8.8)	45	(8.7)
6	23	(8.6)	22	(8.8)	45	(8.7)
7	23	(8.6)	23	(9.2)	46	(8.9)
8	23	(8.6)	23	(9.2)	46	(8.9)
9	24	(9.0)	23	(9.2)	47	(9.1)
10	25	(9.4)	23	(9.2)	48	(9.3)
11	25	(9.4)	23	(9.2)	48	(9.3)
12	26	(9.7)	23	(9.2)	49	(9.5)

The proportion of patients undergoing minor amputations was similar in those receiving vein grafts (9.1%) and prosthetic grafts (10.7%). The proportion of patients undergoing minor amputation in the two treatment groups was also similar for each type of graft material: 10.5% with iloprost (95%CI 6-15) and 7.9% (95%CI 4-12) with placebo in vein grafts and 6.3% with iloprost (95%CI 0-13) and 15.4% with placebo (95%CI 3-27) in prosthetic grafts.

Clinical outcome

The clinical status of the patients at the end of the follow-up showed that over half of the patients had a poor clinical outcome at 12 months. Overall 238 (46.0%) of the patients entering the study were classified as Fontaine stage I or stage II 12 months later, 78 patients (15.1%) were still in Fontaine stage III or stage IV, 105 (20.3%) had been amputated and a further 85 patients (16.4%) had died. The status of 11 patients (2.2%) was not fully documented at the end of follow-up.

The number of patients in each Fontaine stage and those undergoing major amputation or dying is shown below according to treatment group (Table 69). The staging represents the status of the patient at the end of the 12 month follow-up and the last recorded Fontaine stage of those patients who had undergone a major amputation of

the leg in which the bypass had been performed, or of those who had died is not included in this table. There were no significant differences between the iloprost and placebo treated groups at 12 months with respect to Fontaine stage or numbers of patients amputated or dead.

Table 69. Clinical outcome by treatment group at 12 months

Clinical outcome	Number of patients (%)					
	Iloprost n=267		Placebo n=250		Total n=517	
Stage I	90	(33.7)	92	(36.8)	182	(35.2)
Stage II	32	(12.0)	24	(9.6)	56	(10.8)
Stage III	14	(5.2)	19	(7.6)	33	(6.4)
Stage IV	23	(8.6)	22	(8.8)	45	(8.7)
Amputation	53	(19.9)	52	(20.8)	105	(20.3)
Death	53	(19.9)	45	(18.0)	98	(19.0)
Amputation or death	101	(37.8)	89	(35.6)	190	(36.8)
Not recorded	7	(2.6)	4	(1.6)	11	(2.1)

The proportion of patients experiencing the two categories of rest pain was similar in the two treatment groups at all postoperative time points (Table 70). The percentage of patients with no pain at rest increased rapidly from 3.5% pre-operatively to over 60% on day 2 and approached 90% of patients in whom this could be assessed by the end of follow-up. A small proportion of patients (3%-7%) continued to experience continuous rest pain post-operatively. Patients who underwent major amputation or who died were included up to the time of their last assessment of symptoms.

Table 70. Postoperative rest pain by treatment group

Time point	Rest pain	Number of patients (%)					
		Iloprost		Placebo		Total	
Day 2	None	162	(61.8)	157	(63.8)	319	(62.8)
	Intermittent	86	(32.8)	82	(33.3)	168	(33.1)
	Continuous	14	(5.3)	7	(2.8)	21	(4.1)
Day 3	None	169	(64.8)	164	(67.2)	333	(65.9)
	Intermittent	80	(30.7)	74	(30.3)	154	(30.5)
	Continuous	12	(4.6)	6	(2.5)	18	(3.6)
Discharge	None	190	(75.1)	181	(76.1)	371	(75.6)
	Intermittent	56	(22.1)	48	(20.2)	104	(21.2)
	Continuous	7	(2.8)	9	(3.8)	16	(3.3)
3 months	None	172	(78.5)	163	(79.9)	335	(79.2)
	Intermittent	30	(13.7)	29	(14.2)	59	(13.9)
	Continuous	17	(7.8)	12	(5.9)	29	(6.9)
12 months	None	154	(88.5)	144	(86.7)	298	(87.6)
	Intermittent	17	(9.8)	15	(9.0)	32	(9.4)
	Continuous	3	(1.7)	7	(4.2)	10	(2.9)

Use of analgesics post-operatively did not differ greatly between the two treatment groups (Table 71). The continuation of epidural anaesthesia post-operatively was recorded in a small number of patients on days 2 and 3. On day 2 the use of opiate analgesics was also higher than pre-operatively (Table 24), but it was markedly reduced by the time of discharge. The number of patients not taking any analgesics fell immediately post-operatively to 17% from the 20% recorded before surgery, but rose steadily up to 71% three months after surgery. Between three and 12 months the percentage of patients assessed not taking analgesics continued to rise, but the actual number of patients fell in both treatment groups.

Table 71. Postoperative analgesic use by treatment group

Time point	Analgesics	Number of patients (%)					
		Iloprost		Placebo		Total	
Pre-op.	None	68	(25.4)	43	(17.2)	111	(21.5)
	Non-opiates	113	(42.3)	121	(48.4)	234	(45.3)
	Opiates	86	(32.2)	86	(34.4)	172	(33.2)
Day 2	None	45	(17.0)	41	(16.6)	86	(16.8)
	Non-opiates	92	(34.7)	81	(32.8)	173	(33.8)
	Opiates	125	(47.2)	122	(49.4)	247	(48.2)
	Epidural	3	(1.1)	3	(1.2)	6	(1.2)
Day 3	None	70	(26.5)	71	(29.2)	141	(27.8)
	Non-opiates	106	(40.2)	104	(42.8)	210	(41.4)
	Opiates	86	(32.6)	66	(27.2)	152	(30.0)
	Epidural	2	(0.8)	2	(0.8)	4	(0.8)
Discharge	None	126	(49.8)	125	(52.5)	251	(51.1)
	Non-opiates	100	(39.5)	81	(34.0)	181	(36.9)
	Opiates	27	(10.7)	32	(13.4)	59	(12.0)
3 months	None	149	(68.0)	149	(73.8)	298	(70.8)
	Non-opiates	50	(22.8)	34	(16.8)	84	(20.0)
	Opiates	20	(9.1)	19	(9.4)	39	(9.3)
12 months	None	136	(79.1)	136	(82.9)	272	(81.0)
	Non-opiates	27	(51.7)	21	(12.8)	48	(14.3)
	Opiates	9	(5.2)	7	(4.3)	16	(4.8)

Tables 72 and 73 confirm that when the presence of rest pain and analgesic use are looked at together, there are no major differences between the treatment groups at discharge or at 12 months. They also show that at 12 months, there were very few patients who experienced rest pain despite the use of opiate analgesics and also very few who were still experiencing continuous pain at rest with or without analgesics. There were, however, a large number at 12 months who had no pain or analgesic assessment due to amputation or death.

Table 72. Rest pain and analgesic use at discharge

Rest pain	Analgesic	Number of patients (%)					
		Iloprost (n=267)		Placebo (n=250)		Total (n=517)	
None	None	122	(45.7)	124	(49.6)	246	(47.6)
	Non-opiates	60	(22.5)	49	(19.6)	109	(21.1)
	Opiates	8	(3.0)	8	(3.2)	16	(3.1)
Intermittent	None	4	(1.5)	1	(0.4)	5	(1.0)
	Non-opiates	38	(14.2)	32	(12.8)	70	(13.5)
	Opiates	14	(5.2)	15	(6.0)	29	(5.6)
Continuous	None	0	(0.0)	0	(0.0)	0	(0.0)
	Non-opiates	2	(0.7)	0	(0.0)	2	(0.4)
	Opiates	5	(1.9)	9	(3.6)	14	(2.7)
Not recorded	Not recorded	14	(5.2)	12	(4.8)	26	(5.0)

Table 73. Rest pain and analgesic use at 12 months

Rest pain	Analgesic	Number of patients (%)					
		Iloprost (n=267)		Placebo (n=250)		Total (n=517)	
None	None	133	(49.8)	132	(52.8)	265	(51.3)
	Non-opiates	17	(6.4)	8	(3.2)	25	(4.8)
	Opiates	2	(0.7)	1	(0.4)	3	(0.6)
	Not recorded	2	(0.7)	3	(1.2)	5	(1.0)
Intermittent	None	2	(0.7)	3	(1.2)	5	(1.0)
	Non-opiates	9	(3.4)	10	(4.0)	19	(3.7)
	Opiates	6	(2.2)	1	(0.4)	7	(1.4)
	Not recorded	0	(0.0)	1	(0.4)	1	(0.2)
Continuous	None	1	(0.4)	1	(0.4)	2	(0.4)
	Non-opiates	1	(0.4)	2	(0.8)	3	(0.6)
	Opiates	1	(0.4)	4	(1.6)	5	(1.0)
Not recorded	None	0	(0.0)	0	(0.0)	0	(0.0)
	Non-opiates	0	(0.0)	1	(0.4)	1	(0.4)
	Opiates	0	(0.0)	1	(0.4)	1	(0.4)
	Not recorded	93	(34.8)	82	(32.8)	175	(33.8)

In the early post-operative assessments of trophic lesions, the percentage of patients with ulcers was slightly higher in the group of patients treated with iloprost (Table 74), but the magnitude of the differences were similar to the 7% difference in incidence of ulcers noted prior to surgery (Table 25). The numbers of patients without ulcers increased up to three months, but then fell at 12 months, although continuing to rise as a percentage, due to the large fall in the number of patients assessed having ulcers.

Table 74. Postoperative ulcers by treatment group

Time point	Ulcers	Number of patients (%)					
		Iloprost		Placebo		Total	
Pre-op.	Absent	126	(48.1)	134	(48.1)	260	(48.1)
	Present	141	(51.9)	115	(51.9)	256	(51.9)
3 days	Absent	127	(48.1)	133	(54.7)	260	(51.3)
	Present	137	(51.9)	110	(45.3)	247	(48.7)
Discharge	Absent	134	(53.2)	143	(60.6)	277	(56.8)
	Present	118	(46.8)	93	(39.4)	211	(43.2)
3 months	Absent	158	(71.8)	153	(75.4)	311	(73.5)
	Present	62	(28.2)	50	(24.6)	112	(26.5)
12 months	Absent	150	(87.7)	140	(87.0)	290	(87.3)
	Present	21	(12.3)	21	(13.0)	42	(12.7)

The percentage of patients with gangrene was higher in the iloprost group at discharge (Table 75), but once as with the incidence of ulcers, the difference in incidence of gangrene, of the order of 10%, was not very different from the 7% difference observed between the treatment groups before surgery (Table 25). The numbers of patients with gangrene fell throughout the follow-up period in both groups.

Table 75. Postoperative gangrene by treatment group

Time point	Gangrene	Number of patients (%)					
		Iloprost		Placebo		Total	
Pre-op.	None	143	(53.6)	152	(60.8)	295	(57.1)
	Dry	89	(33.3)	70	(28.0)	159	(30.8)
	Wet	20	(7.5)	12	(4.8)	32	(6.2)
	Dry and wet	15	(5.6)	15	(6.0)	30	(5.8)
3 days	None	143	(54.2)	150	(61.5)	293	(57.7)
	Dry	91	(34.5)	69	(28.3)	160	(31.5)
	Wet	16	(6.1)	16	(6.6)	32	(6.3)
	Dry and wet	14	(5.3)	9	(3.7)	23	(4.5)
Discharge	None	146	(57.9)	162	(68.4)	308	(63.0)
	Dry	84	(33.3)	57	(24.1)	141	(28.8)
	Wet	10	(4.0)	10	(4.2)	20	(4.1)
	Dry and wet	12	(4.8)	8	(3.4)	20	(4.1)
3 months	None	182	(82.7)	180	(88.7)	362	(85.6)
	Dry	27	(12.3)	12	(5.9)	39	(9.2)
	Wet	5	(2.3)	7	(3.4)	12	(2.8)
	Dry and wet	6	(2.7)	4	(2.0)	10	(2.4)
12 months	None	166	(97.1)	158	(97.5)	324	(97.3)
	Dry	5	(2.9)	3	(1.9)	8	(2.4)
	Wet	0	(0.0)	1	(0.6)	1	(0.3)

Combining information on ulcers and gangrene to give the presence of any trophic lesions showed a greater number of patients in the iloprost group with lesions at discharge (Table 76). However, the number of patients without lesions rose in both groups during the follow-up and was numerically greater in the iloprost treated group at 12 months. Almost 14% of patients who had not undergone major amputation or died continued to have trophic lesions after 12 months.

Table 76. Postoperative ulcers and gangrene by treatment group

Time point	Ulcers or gangrene	Number of patients (%)					
		Iloprost		Placebo		Total	
3 days	Absent	88	(33.3)	92	(37.7)	180	(35.4)
	Present	176	(66.7)	152	(62.3)	328	(64.6)
Discharge	Absent	96	(38.1)	113	(47.7)	209	(42.7)
	Present	156	(61.9)	124	(52.3)	280	(57.3)
3 months	Absent	145	(65.9)	142	(70.0)	287	(67.8)
	Present	75	(34.1)	61	(30.0)	136	(32.2)
12 months	Absent	148	(86.5)	139	(85.8)	287	(86.2)
	Present	23	(13.5)	23	(14.2)	46	(13.8)

Doppler pressures

Following surgery, arterial pressures measured by Doppler at the ankle or calf were substantially higher in both treatment groups. At discharge measurements were available on 84% of the patients alive without a major amputation and the highest recorded ankle pressures and the ABPI were similar in the two treatment groups (Table 77). At 12 months measurements were recorded on 82% of the patients alive and without a major amputation. At this time point the ankle pressure and the ABPI were somewhat higher in the iloprost treated group (Table 78). Mean ankle systolic pressures at 12 months in surviving limbs were iloprost 145 mmHg (95%CI 137-153) and placebo 136 mmHg (95%CI 128-144). Mean ABPI at 12 months in these patients were iloprost 0.92 (95%CI 0.87-0.97) and placebo 0.86 (95%CI 0.82-0.90).

Table 77. Doppler pressures at discharge

Variable	Iloprost	Placebo	Total
Brachial artery	143 ± 22 (n=207)	142 ± 23 (n=184)	143 ± 22 (n=391)
Ankle: mean ± SD	126 ± 46 (n=202)	124 ± 44 (n=177)	125 ± 45 (n=379)
ABPI: mean ± SD	0.88 ± 0.30 (n=204)	0.87 ± 0.28 (n=179)	0.87 ± 0.29 (n=383)

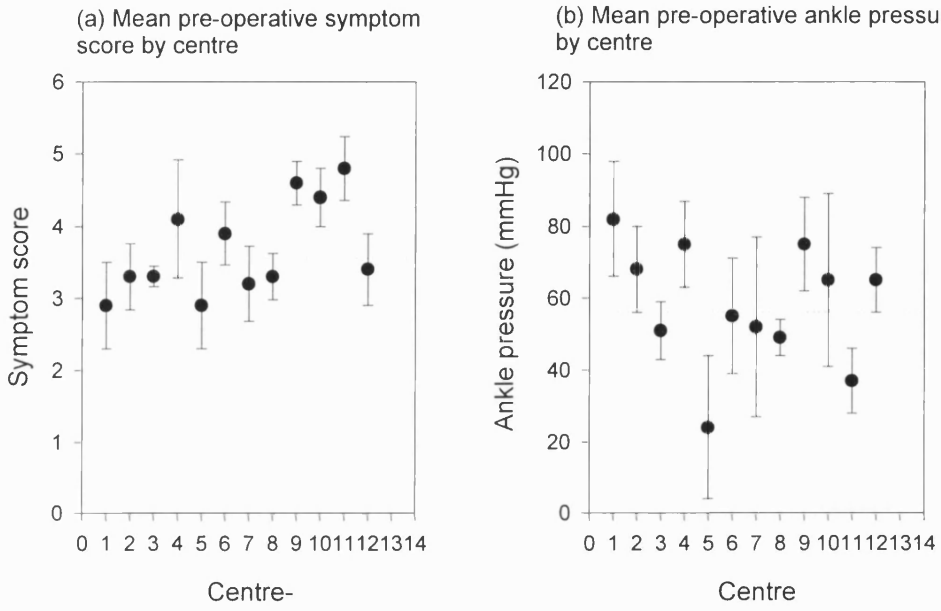
Table 78. Doppler pressures at 12 months

Variable	Iloprost	Placebo	Total
Brachial artery	158 ± 23 (n=139)	157 ± 30 (n=129)	157 ± 27 (n=268)
Ankle: mean ± SD	145 ± 50 (n=137)	136 ± 45 (n=127)	141 ± 47 (n=264)
ABPI: mean ± SD	0.92 ± 0.28 (n=137)	0.86 ± 0.25 (n=128)	0.89 ± 0.27 (n=265)

4.6. Results by trial centre

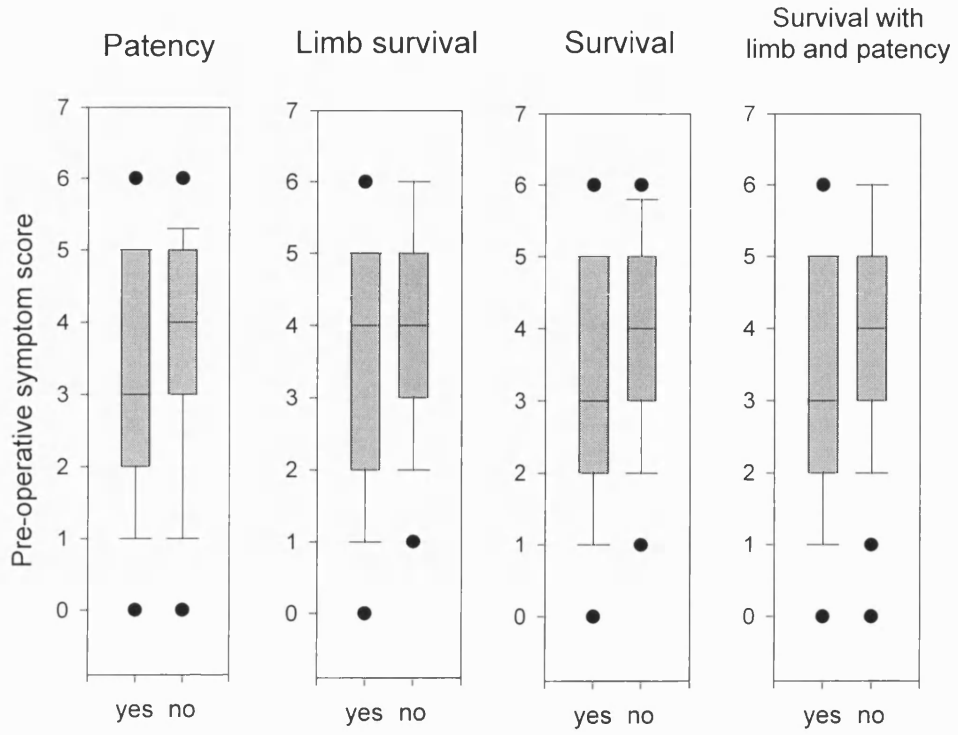
The type of patients entered into the trial in the different participating centres were similar in most respects, but some differences could be observed in the disease severity as indicated by the symptom severity score and the pre-operative ankle pressure (Figure 29).

Figure 29. Measures of disease severity by centre



Although pre-operative disease severity does not necessarily mean a worse outcome in terms of bypass patency, it is more likely to be of importance when considering clinical outcomes as illustrated by the association of the pre-operative symptom score with various outcome measures (Figure 30).

Figure 30. Association of symptom severity scores with various outcome measures. Graphs show median, interquartile range, 10% and 90% deciles and position of outliers.



Patient management also varied between the centres with respect to vein graft surveillance and the use of oral antithrombotic agents after discharge. Vein graft surveillance by duplex ultrasound was optional in the study and not performed at all centres. It was additionally not performed on all patients in those centres which did have the facility and the proportion of grafts in which stenoses were detected varied somewhat between centres (Table 79).

Table 79. Frequency of graft surveillance and incidence of graft stenoses by centre in vein grafts or grafts containing vein segments in eligible patients

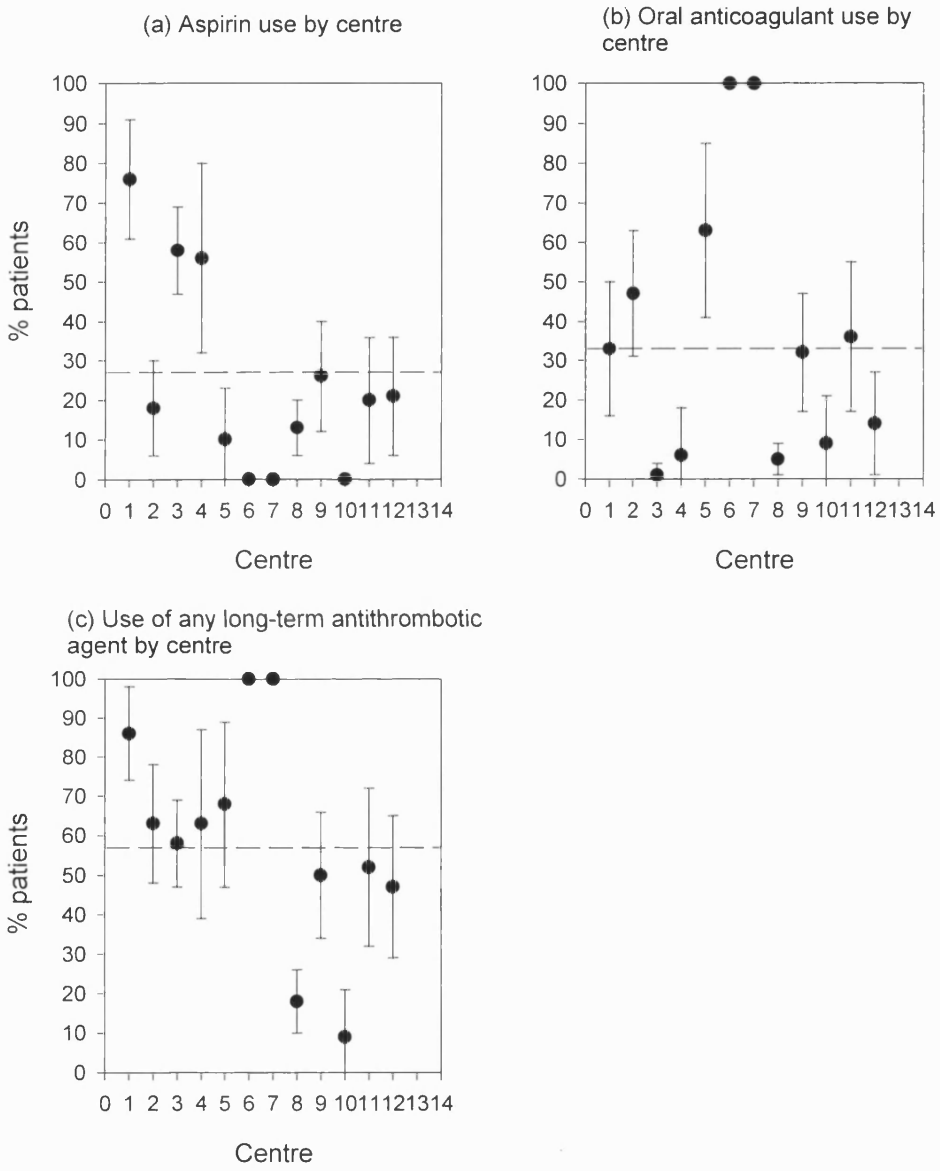
Centre	No. of patients operated and eligible	No. of patients scanned (as % of those eligible)		No. of patients with stenoses (% of those scanned)		No. of patients with composite vein grafts (%)	
1	3	0	(0)		-		-
2	16	15	(94)	3	(20)	0	(0)
3	26	25	(96)	8	(32)	5	(20)
4	5	5	(100)	2	(40)		-
5	59	42	(71)	23	(55)	9	(21)
6	5	1	(20)	0	(0)		-
7	9	8	(89)	3	(38)	1	(13)
8	36	36	(100)	12	(33)	6	(17)
9	10	9	(90)	2	(22)	2	(22)
10	8	3	(38)	2	(33)		-
11	8	8	(100)		-		-
12	72	66	(92)	6	(9)	1	(2)
13	22	14	(64)	1	(7)	0	(0)
14	4	0	(0)		-		-
16	4	4	(100)	0	(0)		-
17	3	0	(0)		-		-
18	17	14	(82)	2	(14)	1	(7)
19	20	18	(90)	4	(22)	5	(28)
20	17	15	(88)	4	(27)	0	(0)
21	1	0	(0)		-		-
22	7	7	(100)	2	(29)		-
Total	352	290	(82)	76	(26)	30	(10)

Four centres included more than 20 patients with vein grafts in the surveillance programme and in these centres the incidence of stenoses detected in vein and vein-prosthetic composite grafts ranged from 9% to 55%. Amongst these four centres, the centre with the highest incidence of stenoses also included the highest proportion of composite vein-vein grafts amongst the grafts scanned: 9/42 (21%) compared to 30/289 (10%) in the study population as a whole and 1/66 (1.5%) in the centre with the lowest incidence of detected stenoses.

Usage of oral antithrombotic agents during the post-discharge follow-up varied greatly, both by centre (Figure 31). Most striking was the almost universal use of oral

anticoagulants in the patients included from the Netherlands (centres 6 and 7 in Figure 31b). The use of aspirin was notably more frequent in the United Kingdom than elsewhere (centres 1, 3 and 4 in Figure 31a) while there was commonly an absence of any long-term antithrombotic medication in a couple of centres (Figure 31c).

Figure 31. Use of long-term antithrombotic agents by centre



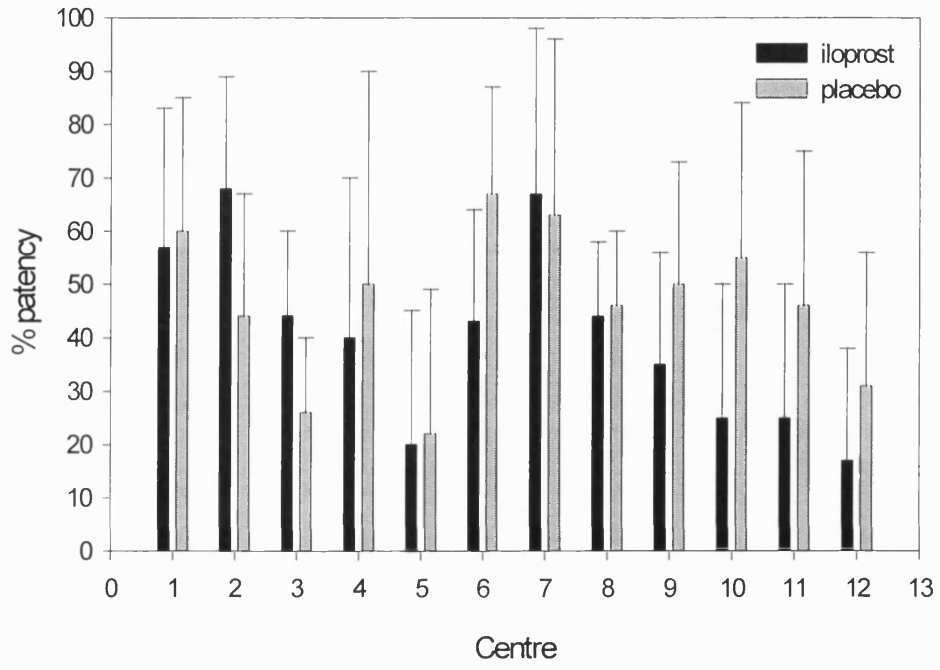
The randomisation of patients to receive either iloprost or placebo was stratified by centre and the distribution of patients in the two treatment groups was therefore well-balanced in each centre (Table 80).

Table 80. Distribution of patients in the two treatment groups by centre

Centre	n	No. of patients (%)	
		Iloprost	Placebo
1	11	6 (55)	5 (45)
2	29	14 (48)	15 (52)
3	37	19 (51)	18 (49)
4	11	7 (64)	4 (36)
5	77	39 (51)	38 (49)
6	16	10 (63)	6 (37)
7	19	10 (53)	9 (47)
8	42	21 (50)	21 (50)
9	17	9 (53)	8 (47)
10	9	5 (56)	4 (44)
11	12	7 (58)	5 (42)
12	100	50 (50)	50 (50)
13	38	20 (53)	18 (47)
14	4	1 (25)	3 (75)
16	8	4 (50)	4 (50)
17	6	3 (50)	3 (50)
18	23	12 (52)	11 (48)
19	23	12 (52)	11 (48)
20	25	12 (48)	13 (52)
21	1	1 (100)	0 (0)
22	9	5 (56)	4 (44)
Total	517	267 (52)	250 (48)

Despite the wide variation in overall individual centre patency and amputation results, there was generally no evidence of superiority of either iloprost or placebo in individual centres (Figures 32 to 35), except in centres 5 and 9 in which the patency appeared respectively better and worse with iloprost. Patency rates varied between treatment groups by as much as 30%, but the confidence intervals indicated the likelihood that the differences may have been random in origin.

Figure 32. Primary patency at 12 months with iloprost and placebo in all patients by centre (percentage with 95% CI). Centres shown are the 12 largest recruiting centres numbered in sequence.



There were few instances in which the primary patency rates calculated for either iloprost or placebo differed significantly between the trial centres (Figure 32).

Figure 33. Differences in primary patency at 12 months between the two treatment groups by centre (iloprost - placebo percentage with 95% CI). Centres shown are the 12 largest recruiting centres numbered by their original centre number.

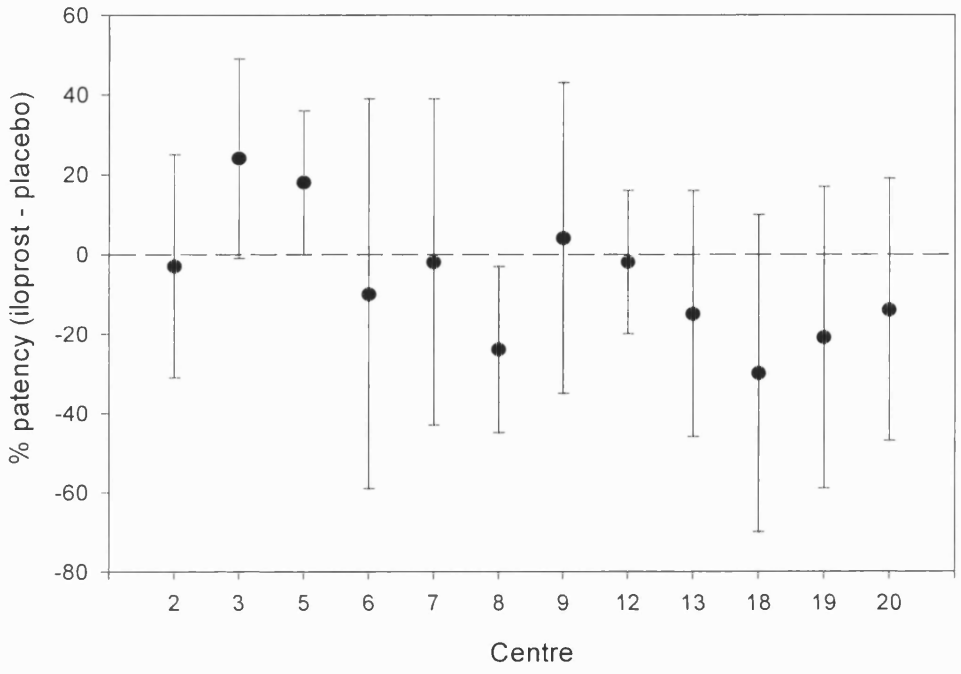


Figure 34. Percentage of patients with major amputation with iloprost and placebo in all patients by centre (percentages and 95% CI). Centres shown are the 12 largest recruiting centres numbered in sequence.

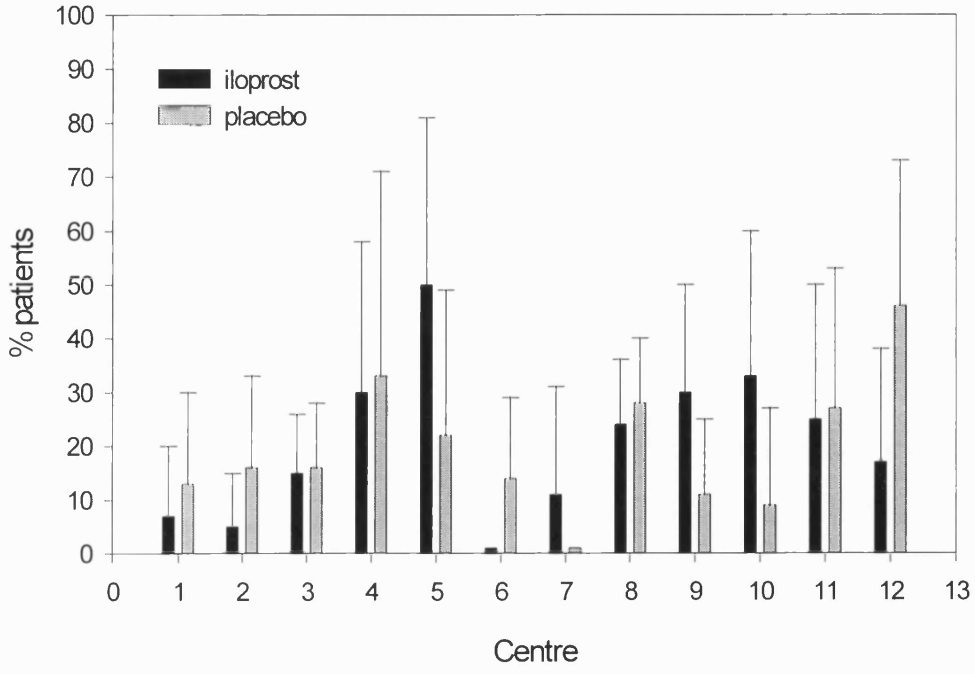
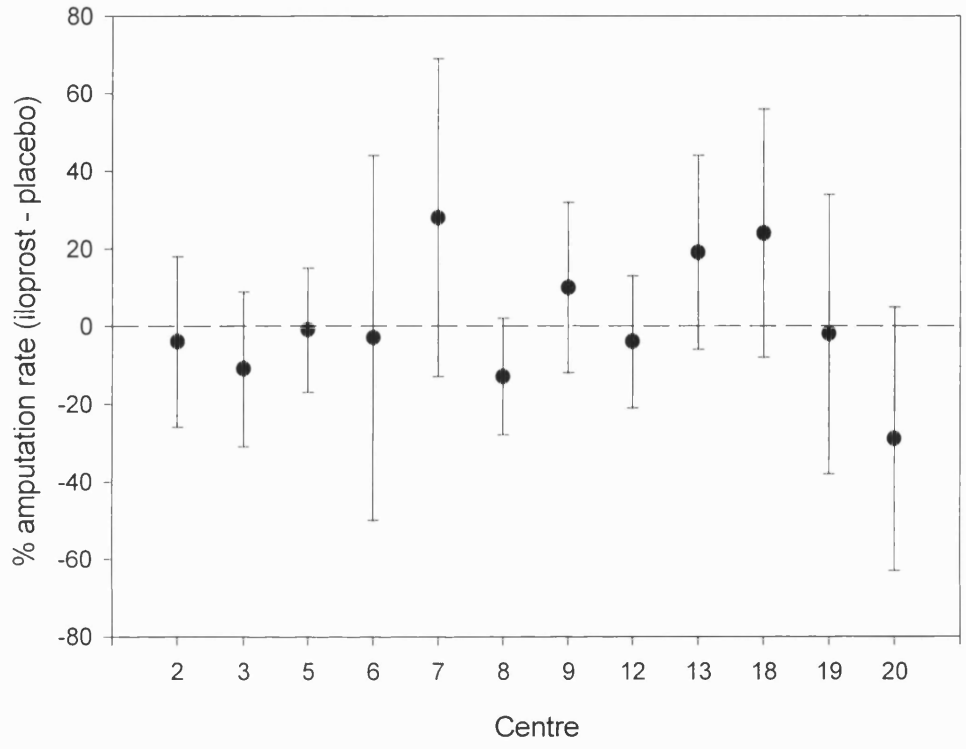


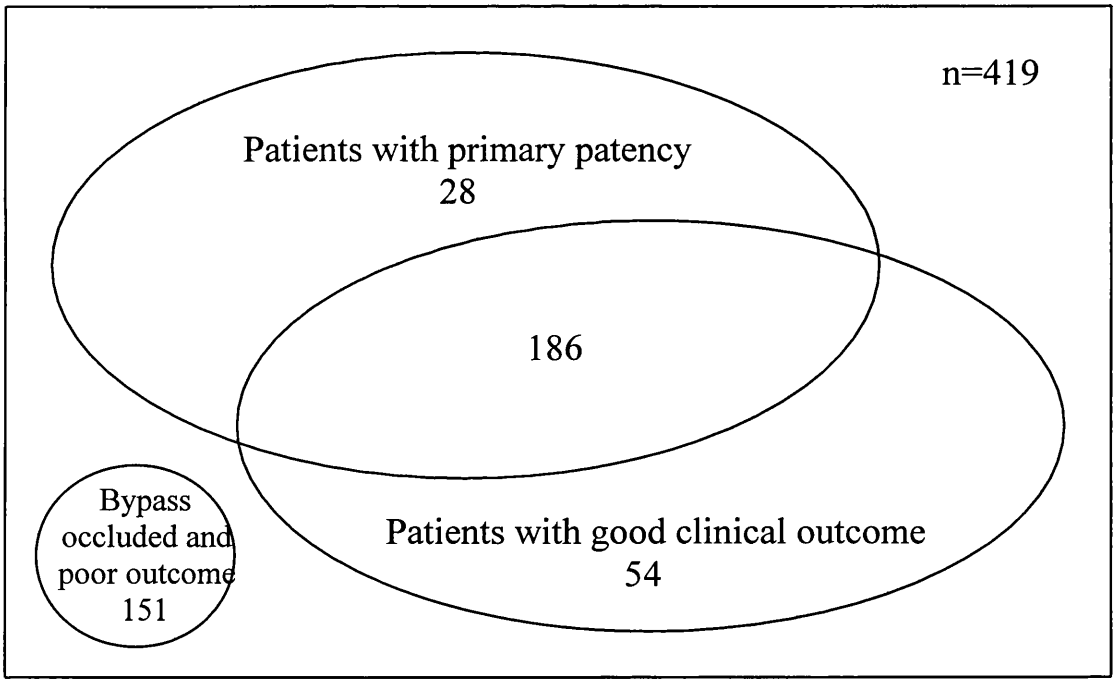
Figure 35. Differences in major amputation rate at 12 months between the two treatment groups by centre (iloprost - placebo percentage with 95% CI). Centres shown are the 12 largest recruiting centres numbered by their original centre number.



4.7. Evaluation of the clinical relevance of the primary efficacy endpoint used in the trial

In order to evaluate the clinical relevance of primary patency of the bypass, the primary endpoint selected for this trial, the association of primary patency with the clinical outcome (irrespective of treatment group) was assessed by classifying each patient as having a good or poor clinical outcome. A good clinical outcome was defined as a patient having an intact limb and peripheral arterial disease Fontaine stage I or II. A poor outcome was a patient in stage III or IV or who had undergone a major amputation of the limb operated. The resulting association of primary patency with clinical outcome is illustrated below for all patients in whom both a clinical outcome and primary patency could be established at 12 months (Figure 36).

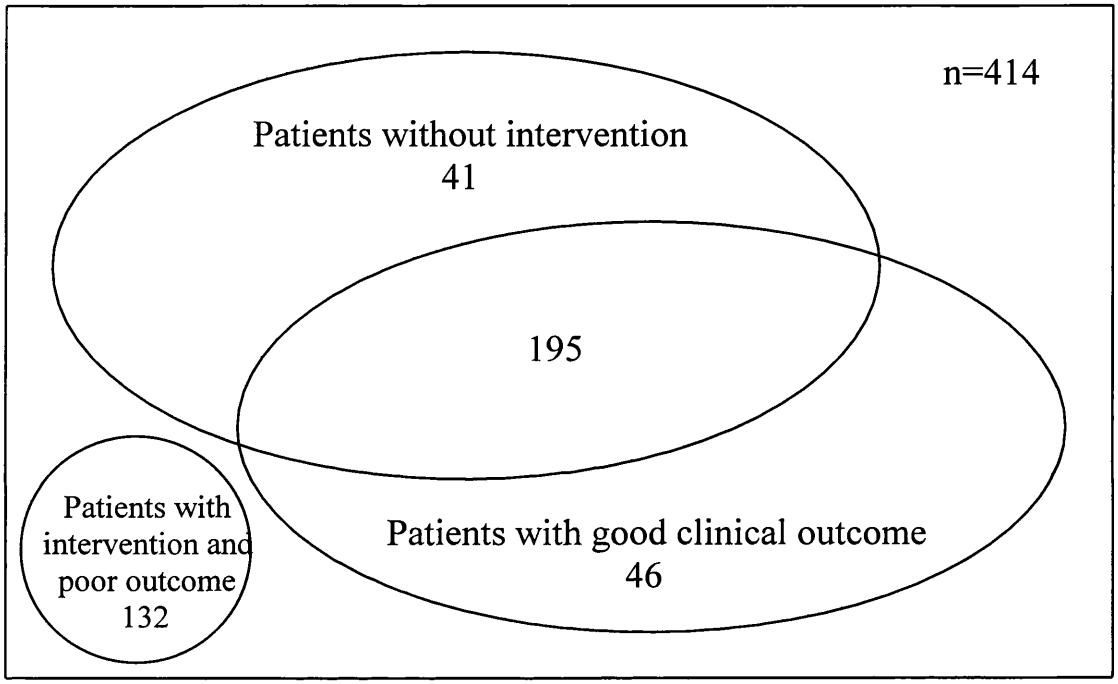
Figure 36. Concordance of patients with primary patency and a good clinical outcome at 12 months



The concordance of primary patency with clinical outcome was thus 80.4% with a false positive rate of 6.7% and a false negative rate of 12.9%. Alternatives to primary patency could be considered as trial endpoints. The number of patients free of any vascular intervention in the relevant limb is another technical endpoint which may convey useful clinical information and composite endpoints including both technical endpoints, amputation and survival may provide a good overall outcome measure.

The extent to which the intervention-free rate represents the patients with a good clinical outcome is shown below for all patients surviving to 12 months or undergoing a vascular procedure prior to that (Figure 37). Information on both interventions and clinical outcome was available for 414 patients. It can be seen that a total of 236 patients were intervention-free, but that 41 of these had a poor clinical outcome at 12 months. These 41 cases could be considered as false positives if being intervention-free is interpreted as a indicative of a good clinical outcome, a false positive rate of 9.9%.

Figure 37. Concordance of patients without intervention and clinical outcome at 12 months

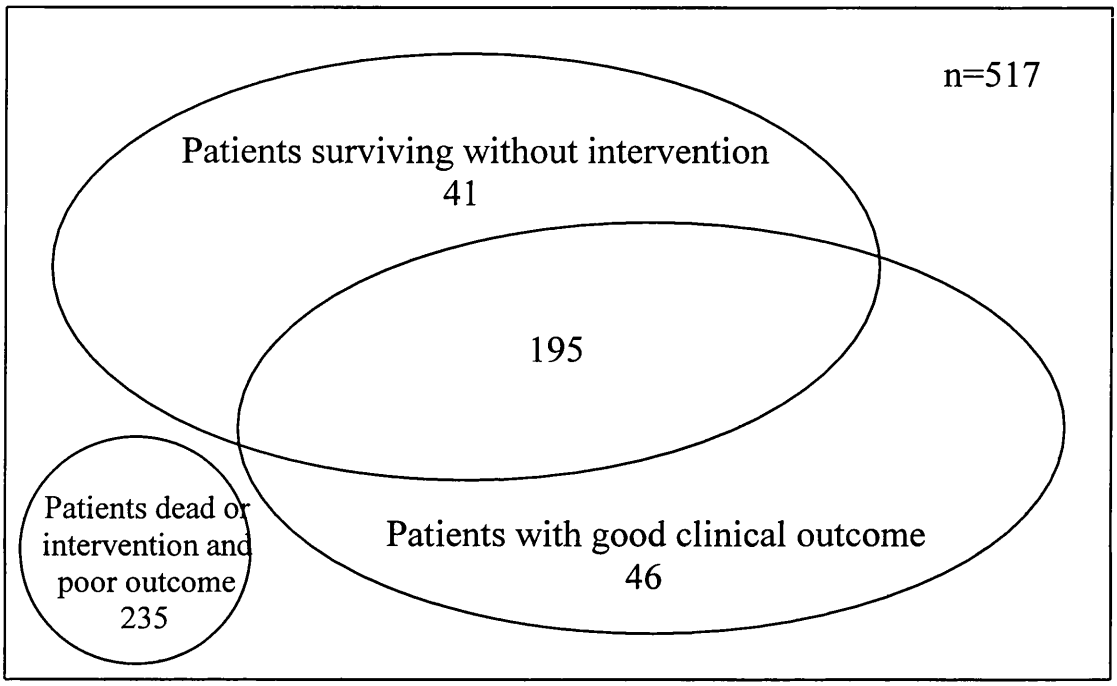


A certain number of the interventions performed could have been indicated, not by clinical symptoms, but according to haemodynamic criteria due to the development of graft stenoses. However, these comprised only a small proportion of the interventions performed in this study and in each of the cases in this study where a dilatation of a graft stenosis was the only intervention performed, the patient had been suffering from persisting or recurring symptoms. There were in effect then no false negatives as the interventions in all 178 patients were indicated by a poor clinical outcome to the initial bypass procedure, even if 46 of them subsequently had a good outcome. There was therefore an agreement of intervention as an endpoint with the clinical outcome from the initial operation in 90.1% of cases.

Combined technical and clinical outcome measures

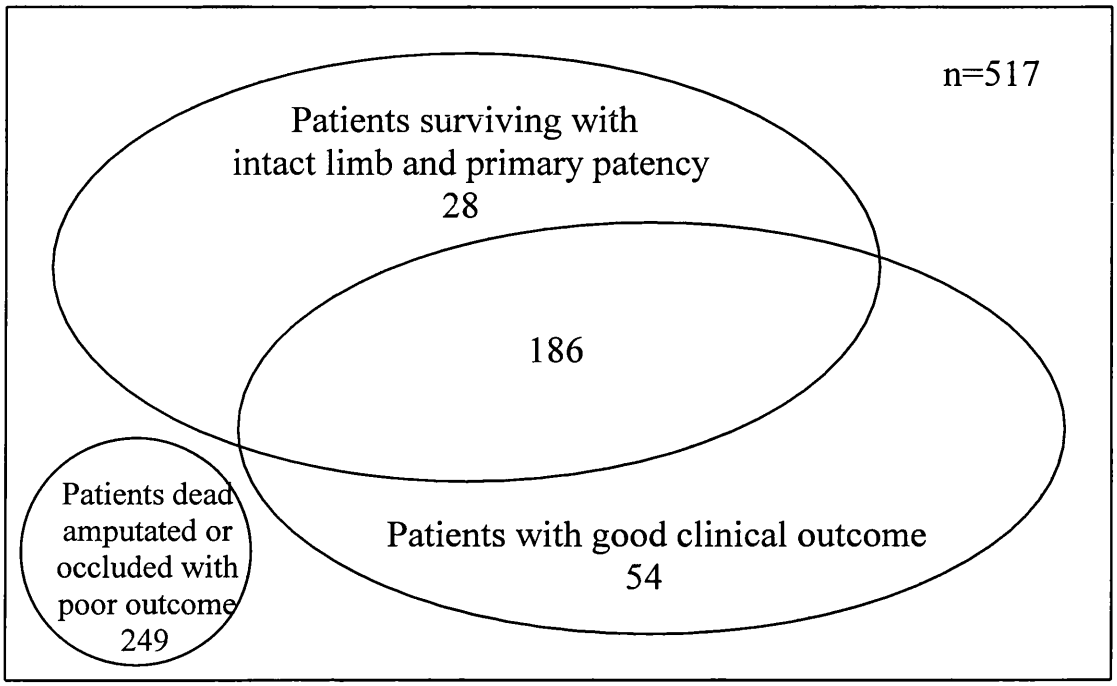
The number of patients in whom the composite endpoint agrees with the clinical outcome is illustrated for patients surviving without intervention (Figure 38) and for patients surviving with an intact limb and primary patency (Figure 39).

Figure 38. Concordance of patients surviving without intervention and clinical outcome at 12 months



The endpoint 'patients surviving intervention-free' showed a false positive rate of 41/517 patients or 7.9% (Figure 38). There are in effect no false negatives as it was assumed that all patients undergoing an intervention would have had a poor outcome without it. The false positive rate was lower for 'patients surviving with an intact limb and primary patency' at 28/517 or 5.4%, but the false negative rate was higher at 54/517 or 10.4% (Figure 39).

Figure 39. Concordance of 'patients alive with an intact limb and primary bypass patency' and clinical outcome at 12 months



Summary of concordance of different endpoints with clinical outcome

The rates of false positives and false negatives which would have occurred taking each of the various technical and composite endpoints as surrogates for clinical outcome measured in terms of Fontaine stage are summarised below including secondary bypass patency which might be expected to be closer to clinical outcome than primary patency (Table 81). The best overall agreement of endpoint and clinical outcome was obtained with patients who were 'intervention-free' or 'surviving and intervention-free'. Excluding patients who had only a PTA of a graft stenosis from those judged to have undergone an intervention, did not improve the agreement of these endpoints with clinical outcome.

Table 81. Rates of false positives and false negatives with various technical and composite endpoints as surrogates for clinical outcome

endpoint	**n**	**false positive % (95% CI)**	**false negative % (95% CI)**	**concordance % (95% CI)**
Primary patency	419	6.7 (4.3-9.1)	12.9 (9.7-16.1)	80.4 (76.6-84.2)
Secondary patency	419	13.4 (10.1-16.7)	5.3 (3.2-7.4)	81.4 (77.7-85.1)
Intervention-free	414	9.9 (7.0-12.8)	-	90.1 (87.2-93.0)
Survival with limb and primary patency	517	5.4 (3.5-7.3)	10.4 (7.8-13.0)	84.2 (81.1-87.3)
Survival with limb and secondary patency	517	10.8 (8.1-13.5)	4.3 (2.6-6.0)	84.9 (81.8-88.0)
Survival intervention-free	517	7.9 (5.6-10.2)	-	92.1 (89.8-94.4)

5. DISCUSSION

5.2. Discussion of iloprost study results

Underlying statistical and clinical assumptions

The study assumed a primary patency rate in the control group of 75% at 12 months and was designed to detect an improvement to 87.5% in the treated group. This represents an absolute improvement of 12.5% in patency and a relative improvement of 16.7% in the success rate or a relative reduction of 50% in the failure rate. The sample size required to demonstrate this with α=0.05 and β=0.10 was calculated to be 221 patients per group. Due to the higher proportion of patients receiving prosthetic grafts than had been expected, almost 18% compared to the expected 10%, the number of vein grafts included in the trial fell slightly short of the desired number with groups sizes of 209 and 215. This modest shortfall resulted in a small loss of power to detect the desired difference. More remarkable was the much lower than anticipated patency rate in the control group.

It is rare to find reports in the literature of a large series of femorodistal vein grafts with such a low primary patency rate at 12 months. Factors which may help to explain this are the inclusion of patients with immediate graft occlusion as loss of primary patency, the strict monitoring and checking of records against the hospital notes by external study monitors, the completeness of the follow-up with very few patients lost and the multicentre design of the study. Also, the very fact of the trial taking place may have led surgeons to operate in more difficult cases in the belief that the study medication would improve the chances in cases which would otherwise have been left or amputated.

A review of the literature found that many trials of adjuvant therapy in peripheral bypass excluded immediate bypass occlusion on the grounds that it is a technical failure and not a failure of treatment. This may also be the case in many reports of uncontrolled surgical series. The checking of trial records against hospital notes helps to ensure a common understanding of, and application of, the agreed definitions in a multicentre trial. This is particularly important in questions where there is room for interpretation, such as in the definition of an intervention and assisted primary patency. The difference in results obtained from a typical surgical follow-up and from the more complete follow-up which can be achieved when a priority is given to this task has been well illustrated by Jensen *et al* (1996) who showed a reduction in primary patency from 68% in their surgical registry to 52% in a controlled trial. It should not therefore be assumed that those patients successfully followed in this surgical indication are representative of all those entered into a trial.

The multicentre nature of this trial compared to the single centre nature of many published research projects may also partly account for the poorer than expected results.

There is a recognised publication bias in favour of larger and more positive studies and this may also extend to the uncontrolled surgical series. A small series is less likely to be published than a large one and a surgeon may be more interested in publishing a set of good results than a bad run of results. Since this study included data from small centres as well as large centres, these biases together with the other factors discussed would lead to an overoptimistic assessment of primary patency in these procedures when based solely on reports in the literature.

In the light of the measured primary patency rate in the control group, calculations can be made of the power of the study to demonstrate that the differences observed were real and of the sample size which would have been required to demonstrate a treatment effect of the desired magnitude in this situation (Table 82).

Table 82. Effect of statistical assumptions on sample size with α=0.05 and β=0.10

Assumption	Patency in control group	Patency in treated group	Sample size required
Original protocol assumptions	75.0%	87.5%	221
Actual result in vein grafts	51.8%	52.3%	210,193
Actual result in prosthetic grafts	41.9%	46.0%	3,127
Desired absolute 12.5% reduction in failure rate	51.8%	64.3%	342
Desired relative 50% reduction in failure rate	51.8%	75.9%	90
Desired relative 16.7% increase in success rate	51.8%	60.4%	721

The data in Table 82 illustrate that the difference between the expected patency rate in the control group and the patency rate observed in the control group has different effects on the required sample size depending on how the underlying assumptions are derived. Do a certain proportion of the whole population fail because of poor blood flow, or is it a certain proportion of those failing which do so because of poor blood flow? This distinction is important if the patency rate in the control group turns out to be quite different from that expected. An assumption that 12.5% of all grafts may fail due to factors which can be prevented by an improvement in graft blood flow leads to the requirement for a larger sample size of 342 patients. If, on the other hand it is expected that half of all graft failures (irrespective of how many fail) are preventable by this means, then the larger number of failures provides a larger target to shoot at and the sample size requirement is greatly reduced. Lastly, if the assumption is based on the relative increase

in the number of patent grafts, then a significantly larger number of patients will be required.

There was in fact an additional factor which was important in constructing the original assumptions of this study and that was the minimum effect which would be clinically worthwhile. It was considered that an absolute improvement of 10% in primary patency at 12 months was the least which would be required to make use of the treatment attractive. This was combined with the expectation that early graft failures (between 2 days and 3 months after surgery), which account for about half of all failures in the first 12 months, would be those amenable to prevention with the treatment. It was, therefore, decided to design a study capable of detecting an absolute improvement of 12.5% in the patency rate, assuming a control rate of 75%. In view of the greater than expected occlusion rate observed in the control group, it might have been expected that an effective agent acting in the desired manner would have produced a larger absolute improvement in primary patency. This was not found to be the case. Additionally, the 95% confidence intervals indicate that any real benefit from iloprost treatment on the primary patency of femorodistal vein bypass procedures is unlikely to exceed an 8.8% absolute improvement.

Comparability of treatment groups

The two treatment groups were found to be broadly well-matched in terms of their demographic and pre-operative disease characteristics. Four differences between the groups are worth exploring for their possible influence on post-operative outcome. There was a 3.3 % higher incidence of smokers in the placebo group, 5.2% more women in the iloprost group, 3.6% more patients in Fontaine stage IV in the iloprost group and, related to this, a significantly greater percentage (9.8%) of patients with both ulcers and gangrene in the iloprost group. Of these factors, only the proportion of women receiving bypasses has been shown to be associated with the patency of vein grafts (Magnant *et al* 1993). Both the presence of trophic lesions and smoking, however, have been linked with limb salvage and survival (Woodburn *et al* 1996).

The magnitude of the imbalances in distribution between the groups with respect to sex and smoking seem unlikely to have significantly prejudiced the outcome of the trial on their own. The strong association of pre-operative disease severity with limb salvage after peripheral bypass surgery previously reported (Woodburn *et al* 1996) suggests that the possible influence on amputation rates of the disparity in incidence of trophic lesions should be considered.

The difference in prognosis of vein grafts and prosthetic grafts was accounted for by analysing the technical outcome with the two graft materials separately. Other differences between the groups in technical aspects of the bypass procedures were restricted to the diameter of the vein grafts, which appeared to be smaller in the iloprost group. A smaller vein graft diameter has previously been linked to a poorer long-term patency of reversed vein femoro-infrapopliteal grafts (Wengerter *et al* 1990) and may have influenced the comparison of the two treatment groups.

Treatment and post-operative management

The number of patients in whom the treatment was interrupted or discontinued early was small, such that it should be considered that the planned treatment regimen was adequately tested.

As in earlier studies of an intragraft injection of iloprost, there was a transient, but significant decrease in systolic and diastolic pressure for a few minutes after the intra-operative administration (Hickey *et al* 1991). The longer intravenous infusions given post-operatively in this study could, if a similar effect was produced, have given rise to a steal phenomenon and a reduction in flow through the bypass graft in some patients. This may have masked any benefit derived by other patients. In order to investigate this possibility, analysis of patency was undertaken dividing patients into those who had experienced falls in blood pressure and those who had not. No influence of blood pressure changes on bypass patency was found.

Other antithrombotic agents were given to about 65% of patients at some stage during the follow-up period. More patients received oral anticoagulants than antiplatelet agents. Aspirin was used in 5.7% less patients in the iloprost group than in the control group. Antiplatelet drugs have been shown to reduce the likelihood of peripheral bypass graft occlusion (Antiplatelet Trialists' Collaboration 1994b), suggesting that this difference could have exerted some influence on the investigation of a treatment effect on bypass patency.

Bypass patency

The success of a femorodistal bypass operation for severe ischaemia can be judged in terms of bypass patency, avoidance of amputation and resolution of the clinical symptoms. The first two of these criteria are those which are most commonly reported in the literature. Patency rates reported for femorocrural bypass have improved over time, but more recent literature reports still range for example from 45% in prosthetic grafts (Sayers *et al* 1994) to 87% in vein grafts (Porter 1993) at 12 months. It is often difficult to

know if results being quoted are true primary patency rates or include assisted primary patency or refer to secondary patency. The majority of reports come from single centres and differences in patient selection, surgical technique and follow-up also contribute to the variation in results reported. However, a consistent feature of published series is that much better results are obtained with vein grafts than with prosthetics. A surprising feature of the primary patency rates in this study, therefore, was that the difference between the two materials was only 7.0% at 12 months on life-table analysis. Most reported series quote higher patency rates in vein grafts, but the inclusion of over 400 such procedures in this study from over twenty specialised vascular centres leads to the conclusion that these results are representative of the general situation. The findings are lent additional weight by the fact that the study was independently monitored and produced 12 month follow-up data on patency in over 97% of the cases operated.

Patient selection and clinical outcome

All of the patients included in this trial were deemed by the operating surgeons to be critical. It is clear that all of the patients had severe lower limb ischaemia, but interesting to note that almost half of the patients failed to comply with the European consensus for the definition of critical ischaemia (European Working Group on Critical Leg Ischaemia 1991). This clearly makes comparison with other series difficult, but more importantly raises serious questions about the correct definition of critical ischaemia in relation to reconstructive surgery.

The limb salvage rate after bypass surgery was also not significantly influenced by iloprost treatment. The overall major amputation rate of 20.3% at 12 months is comparable to many published studies (Harling *et al* 1987), but should probably be considered in the context of the overall clinical outcome. In addition to the patients who underwent amputation, 16.4% died in the course of the follow up and 15.1% were still suffering from severe ischaemic symptoms at 12 months. Less than half of the patients had an improved clinical status 12 months after the operation. Clinical outcome in patients undergoing bypass surgery is rarely reported and assuming that these results are typical, it suggests that bypass patency does not always result in an improved clinical outcome. The results concerning mortality, amputation rate and clinical outcome are very similar to recent results from a Swedish population based vascular surgical registry supporting the generalisability of the findings (Bergqvist *et al* 1994).

Study design

Previous studies with iloprost in this indication have shown dramatic effects on distal resistance and graft blood flow (Hickey *et al* 1991, Smith *et al* 1992) and evidence of a beneficial effect on bypass patency (Smith *et al* 1993). There are a number of differences between the earlier studies and the present study. The most striking one is that this study is much larger and in this respect more likely to reflect results when iloprost is used widely. However, all of the studies were placebo controlled and double blind and there are other factors which may influence this conclusion. The treatment regimen in the earlier studies consisted of only a single intra-graft injection of iloprost, whereas in this study three post-operative intravenous infusions were also given. It had been expected that the addition of post-operative infusions would confer an additional benefit due to the improvement of tissue perfusion and the anti-thrombotic effect of iloprost, but it is also conceivable that a tendency to lower the systemic blood pressure resulted in a steal phenomenon in some patients masking the benefit derived in other cases. Analysis of early patency by decreased blood pressure did not support this argument, but a more subtle steal effect cannot be ruled out.

The other major differences between the study designs relate to the fact that the earlier studies were performed in single centres with consistent policies on patient selection, surgical technique and anaesthetic regimen, whereas this study was performed in 21 vascular surgical centres. Although all centres adhered to a strict study protocol with criteria for patient inclusion in the study, there was no way of standardising the original decision that the patient was suitable for a femorodistal bypass procedure. It is also inevitable that there were differences in preferred surgical techniques and concomitant medications. However, the various techniques were generally evenly distributed between the two treatment groups, other than the use of vein or prosthetic grafts, and there are currently no known interactions between iloprost and other concomitant medications used in this study.

The inclusion of prosthetic grafts in a study primarily designed to investigate the use of iloprost in vein grafts was unavoidable due to the initiation of treatment pre-operatively. It is not always known in advance of the operation if the patient's vein will be of sufficiently good quality to provide a conduit. The decision to use prosthetic material may therefore be made during the operation after the patient has been randomised and the study treatment initiated. In these circumstances, even if the treatment were terminated as soon as it was known that the patient would receive a prosthetic graft, the patient would have to be followed up according to the study protocol, in order to monitor the safety of the treatment which had been given. Intention-to-treat analysis might also

be interpreted to dictate that these patients would have to be included in the analysis of bypass patency. Since it was thought that the prosthetic grafts might also benefit from iloprost treatment, the most straightforward solution was to establish *a priori* that all patients randomised would receive the full treatment regimen, but that those receiving vein grafts would be analysed separately from those receiving prosthetic grafts. It was anticipated that prosthetic grafts would comprise only ten per cent of the study population and that the analysis of them would not, therefore, give a very precise estimate of the treatment effect.

Conclusions of iloprost study

In this study no beneficial effect of iloprost was shown in patients receiving vein grafts. Although not the primary objective of the study, a reduction in prosthetic graft failure by iloprost was shown in the immediate post-operative period offering the possibility that a longer term benefit might be shown in such cases if the duration of treatment could be extended. The two groups were generally well balanced, but differed slightly in three respects: the proportion of females, vein graft diameter and use of aspirin. The extent to which these characteristics are might influence the comparison of patency rates is disussed in the next section.

5.2 Discussion of trial methodology

Adjuvant medical therapy in peripheral bypass surgery

It has been pointed out previously that peripheral vascular bypass grafts are an excellent model for evaluating antithrombotic therapy (Society for Vascular Surgery Ad Hoc Committee on Clinical Research 1992). Compared to CABG procedures patency is easier to establish and only one graft is performed per operation. Nonetheless, the review of the literature in this field showed that many drug trials have not been well-designed by current standards of clinical research. Although there seems to be good evidence for the use of aspirin in prosthetic bypass grafts and for another platelet inhibitor, ticlopidine, in autogenous saphenous vein grafts, the wider use of these and other agents for the maintenance of peripheral bypass grafts cannot be justified on the basis of current evidence. Principal criticisms of the trial methodology employed concerned the patient selection criteria, the lack of double-blind design and placebo controls, and the lack of information on clinical outcome.

Patient selection

Patient selection in clinical trials may be categorised as inclusive or exclusive (Sniderman 1999). An inclusive design will lead to patient selection largely on the basis of having the right disease or in the case of surgery, undergoing broadly the same type of procedure. Such a trial will tend to be larger, but may leave open questions concerning benefit or lack of benefit in specific sub-groups, such as different graft materials in bypass surgery. It is necessary in such a trial to categorise the patients with respect to potentially relevant determinants of outcome in order to be able to investigate this question. An exclusive design will study effects in a more narrowly defined group of patients, for example, patients receiving femorotibial vein grafts with single vessel run-off. In this case the specific benefit of the drug will be clear, but the generalisability of the findings to other patients with the same disease but undergoing different procedures is not possible.

The composition of the patient groups can influence markedly the likelihood of attaining good surgical and clinical results. The importance of severity of disease was probably underrated in the iloprost trial as entry was restricted to patients with rest pain or trophic lesions. Inclusion of patients with intermittent claudication adding to the range of disease severity has enabled other authors to show more clearly the importance of symptom severity for clinical outcome (Belkin *et al* 1995, DeWeese *et al* 1977, Rafferty *et al* 1987) and also sometimes an association with patency (Ameli *et al* 1988, Lawson *et al*

1999). If these are to be endpoints of the trial or contribute to a composite primary endpoint, then there needs to be some balance in the symptom severity.

Including a mixture of patients with rest pain and those with trophic lesions makes it difficult to measure the balance of different symptoms between treatment groups. A single scoring system summarising the disparate pre-operative symptoms could be used either to stratify the randomisation of patients, in a process of adaptive randomisation to ensure balanced groups or to explore the influence of symptom severity as an aid to testing the robustness of the trial results. The symptom scoring systems utilised here appeared to be relevant to the clinical outcome and proved easy to apply in different surgical centres due to the unambiguous nature of the classifications. Extending the scoring system to include patients with intermittent claudication would increase the usefulness of such a score as few studies concentrate exclusively on patients with rest pain and trophic lesions.

The observation that different graft materials give differing patency results in distal procedures is not new, but this series indicates that the difference after 12 months between vein and prosthetic grafts may be smaller than suggested by other studies (Tilanus *et al* 1985). It was also found that composite vein-vein grafts gave notably poor results compared to grafts of a single vein segment, and no better than those obtained with prosthetic materials. The inclusion of these grafts may have partly explained the small overall difference between vein and prosthetic grafts. This may be linked to the higher incidence of stenoses found in the composite grafts and poor quality of the conduit rather than the fact of having an extra anastomosis *per se*. This factor is probably less important in trials of shorter and more proximal bypass grafts where prosthetic material yields better results and composite vein grafts are rare. In trials in femorodistal bypasses, it could be considered whether composite grafts should be excluded in order to avoid the risk of unbalancing the treatment groups due to unequal distribution of the small numbers of these grafts between the treatment groups. This was arguably a weakness in the design of the iloprost study.

Perhaps more importantly for clinical trials of drugs designed to reduce graft failure, the meta-analysis of published platelet inhibitor trials presented here indicates that some drugs may be effective in one type of graft, but not in another. Such effects need to be investigated in prospectively planned analyses, as in the iloprost trial, or in separate trials. This is a weakness in about half of the published trials. In the absence of such information, meta-analysis of published trials may help to establish the value of treatment in important subgroups of patients.

Study design

The difference in the results of the smaller single centre iloprost studies and the larger multicentre study is not unusual in clinical drug development. It may be partly explained by the exclusive nature of the initial single centre studies and the inclusive design of the larger multicentre study. Whilst it is possible that the assumption that graft blood flow was an appropriate surrogate variable was misplaced and that the results from two small studies were due to statistical chance. It might also be concluded that the results obtained in the initial studies (Smith *et al* 1993) were not wrong, but that they were simply not applicable to the larger and less homogeneous population of patients undergoing distal bypass procedures in the average vascular centre. Support for this interpretation can be found in the observation that centre 5 in the multicentre iloprost trial, which performed one of the earlier studies (Hickey *et al* 1992), reproduced their earlier result with a 20% higher patency rate with iloprost than with placebo. Few (12%) of the published studies of adjuvant therapy reviewed had a multicentre design and this is a drawback when considering the applicability of the results to patients treated in other centres.

The question of sample size is related to this as single centre studies tend to be smaller due to the time taken to accumulate a sizeable series of patients in one centre. Many of the studies reviewed had an inadequate sample size for the drug effect which could realistically be anticipated. A distinction though should be drawn between studies in vein grafts and those in prosthetic grafts as the prosthetic graft studies had much higher failure rates in the untreated control groups (Green *et al* 1982, Goldman *et al* 1983, Donaldson *et al* 1985), reducing the sample size requirements.

Multicentre trials are preferable in establishing the general applicability of results obtained from single centre studies. In multicentre trials it remains important to avoid as far as possible the inclusion of centres with small numbers of patients. This can unbalance the study by failure to complete randomisation blocks leading to bias due to an individual surgeon's influence through patient selection and operating techniques. Small numbers of cases per centre also make the investigation of any centre effect more difficult due to the resulting wide confidence intervals.

The lack of effect of iloprost in this multicentre trial has been attributed to the inclusion of a heterogeneous population and inconsistent surgical policies (Shearman *et al* 1997). However, this explanation could not be substantiated with the information available on the centres. Despite the various differences between the centres in patients and procedures, most of the individual centres did not differ from each other in the treatment effects shown with iloprost. The intercentre differences in disease severity and

choice of surgical procedure leave the possibility of such differences in outcome in future studies and should be investigated in multicentre trials in this indication. However, there are certain methodological problems in comparing the results in different centres. The sample size is often small resulting in wide confidence intervals. Differences in the completeness of the data is a further problem covered in another section. Similar problems have been pointed out to influence medical audit (Elfström *et al* 1996), and the data presented here emphasise the difficulty in collecting information on sufficient numbers of patients to be able derive meaningful conclusions about the success of certain types of surgical procedures in individual centres. In spite of a patient recruitment phase lasting 18 months, the median number of patients entered per centre was just 17. Not all femorodistal bypass procedures performed over this period will have been entered into the study, but the exclusion criteria were as few as possible without compromising patient safety and the scientific validity of the study. In addition, no other pharmacotherapeutic studies were known to be running in this indication in the centres participating and difficulty in obtaining patient consent was not raised as a major issue limiting recruitment of patients. It seems likely that on average about 50% of the patients undergoing such femorodistal bypass procedures at the participating centres were entered into the study, although the range may have been very large. A register of all eligible patients operated at the participating centres during the recruitment period would have been of interest, but was not compiled in this trial.

It is desirable to identify 'good' surgical centres for clinical trials in order to be sure that benefits of new therapeutic approaches are not masked by surgical deficiencies, but it is clearly difficult to collect sufficient results from individual surgeons or centres to be sure of reaching reliable conclusions about the technical and clinical outcomes. Additional data which could help to assess the centres in future studies would be previous data on the number and outcome of similar operations and data on the patients excluded during the duration of enrolment into the trial.

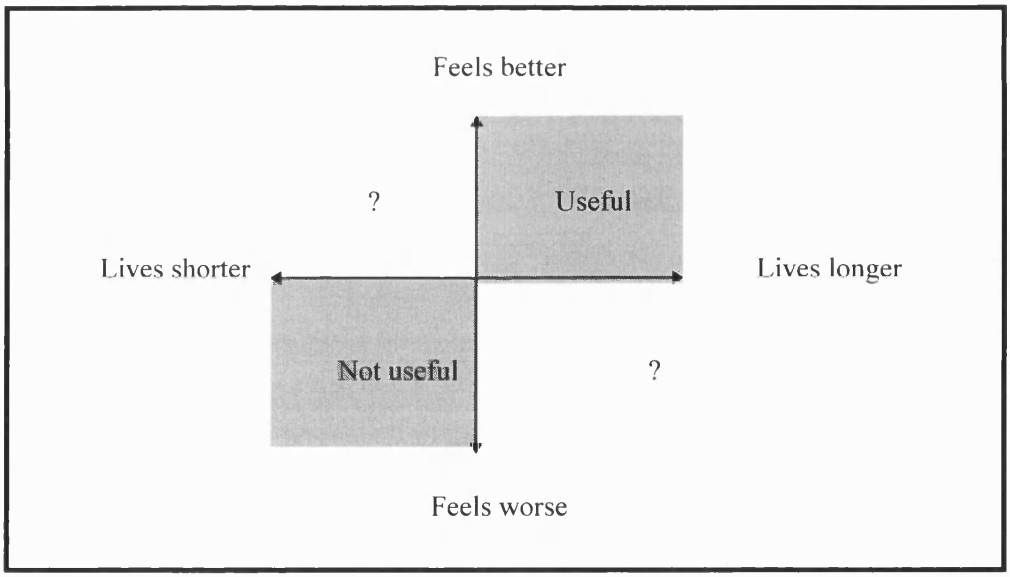
A criticism of the iloprost study could be that half of the centres recruited less than the planned minimum of ten patients per centre. Whilst overall patency and clinical event rates varied more widely amongst the smaller centres, the three largest centres produced iloprost effects on patency which varied from significantly better than placebo to significantly worse. Data from the larger centres also emphasised the differences which can emerge in the characteristics of the patients included by different centres even though they are following a common trial protocol. This serves once again to emphasise the case for multicentre trials to provide findings of general clinical relevance.

An alternative approach to assessing the effectiveness of a new treatment in a variety of surgical centres is to perform a meta-analysis of the data from a number of single centre trials. However, where heterogeneity between the results of different studies exists, this should be investigated wherever a plausible explanation exists (Thompson *et al* 1994). This was illustrated with the example of aspirin studies in peripheral bypass.

Study endpoints

The usefulness of a new drug for the treatment of almost any condition can be determined by the answers to two questions: Does the treatment increase the likelihood of living longer? And does it make the patient feel better? This is essentially a quantity versus quality issue and can be represented graphically (Figure 40). Answers which place the treatment in the upper right or lower left quadrant are clearly useful or not useful, respectively, while treatments in the other two quadrants may be useful in some patients or under certain conditions.

Figure 40. Usefulness of a treatment expressed as its effect on the patient



From reports in the vascular surgery literature, it is often difficult to assess the impact of distal arterial reconstructions on the patients. It has been proposed that the clinical outcome should be included in studies dealing with lower extremity ischaemia (Rutherford *et al* 1997) and exceptionally studies report clinical outcomes in detail (Ray *et al* 1995).

Usually, however, bypass patency and limb salvage results are the only data on which the success of distal arterial reconstructions are judged. The large increase in ankle pressure recorded after a successful distal reconstruction in a severely ischaemic limb (Harling *et al* 1987) leads to the expectation that a rapid improvement in the clinical symptoms would follow and this is probably the reason why bypass patency is generally assumed to be a sufficient guide to the success of the intervention. Patency has been the most commonly reported endpoint in clinical papers and was the primary endpoint chosen for the multicentre trial of iloprost. Unfortunately bypass patency does not tell us that the patient feels better or that he will live longer. The bypass patency does, however, give us some information on the likelihood that the patient will feel better due to the association of patency with clinical outcome in terms of Fontaine stage and major amputation. Patency can be best characterised then as an intermediate or surrogate measure for a patient feeling better.

Patency as a surrogate endpoint

A surrogate endpoint has been defined by Temple (1995) as follows:

> 'a surrogate endpoint of a clinical trial is a laboratory measurement or a clinical sign used as a substitute for a clinically meaningful endpoint that measures directly how a patient feels, functions or survives. Changes induced by the therapy on a surrogate endpoint are expected to reflect changes in a clinically meaningful endpoint'.

From the practical point of view in designing a clinical trial, the ideal surrogate endpoint should be sufficiently sensitive to demonstrate a treatment effect and clinically relevant (Weihrauch *et al* 1998). In addition, several authors have proposed criteria for establishing the value of a surrogate endpoint. Boissel *et al* (1992) stipulated three conditions which should be fulfilled before an endpoint can be considered as a valid substitute for a reliable clinical endpoint:

(1) Convenience. It should easy to evaluate and manifest more frequently than the corresponding clinical endpoint.

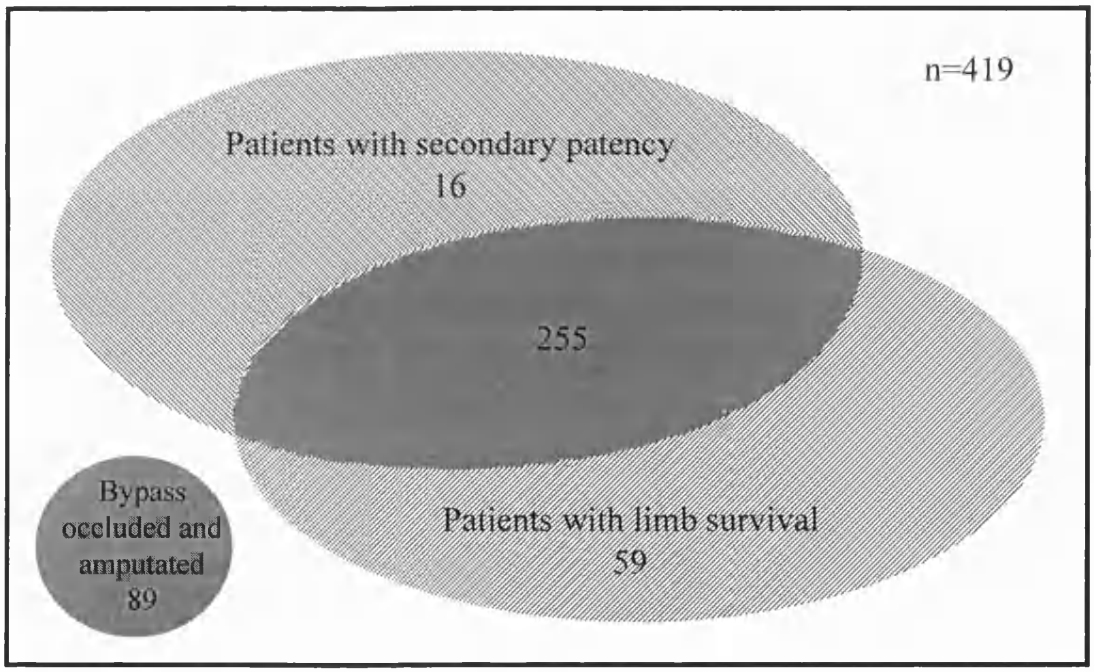
(2) Relationship. The relationship between the surrogate and clinical endpoints should be well established, both qualitatively and quantitatively, on the basis of pathophysiological and epidemiological studies.

(3) Assessment of clinical benefit. An assessment of the degree of clinical benefit to be anticipated should be deducible from the change in the surrogate endpoint.

There is some overlap between these criteria and statements in the ICH guidelines on clinical trials, which consider that the strength of evidence for accepting surrogacy depends upon the biological plausibility of the relationship, the demonstration in epidemiological studies of prognostic value for the clinical outcome and evidence from clinical trials that treatment effects on the surrogate correspond to treatment effects on the clinical outcome (ICH Expert Working Group 1998).

Fleming *et al* (1996) considered that for a surrogate endpoint to be valid as a primary endpoint in a definitive trial, the concurrence of surrogate and clinical outcomes should be very close with the occurrence of false positive and false negative results being low, typically in the range of 2.5% to 10%. Figure 41 illustrates the concordance of bypass patency and limb survival in patients in the iloprost study excluding those in whom neither endpoint could be assessed due to death.

Figure 41. Concordance of secondary bypass patency and limb survival at 12 months amongst patients alive and followed up in the iloprost study. The solid shading represents the 82.1% of cases with agreement between patency and limb survival.

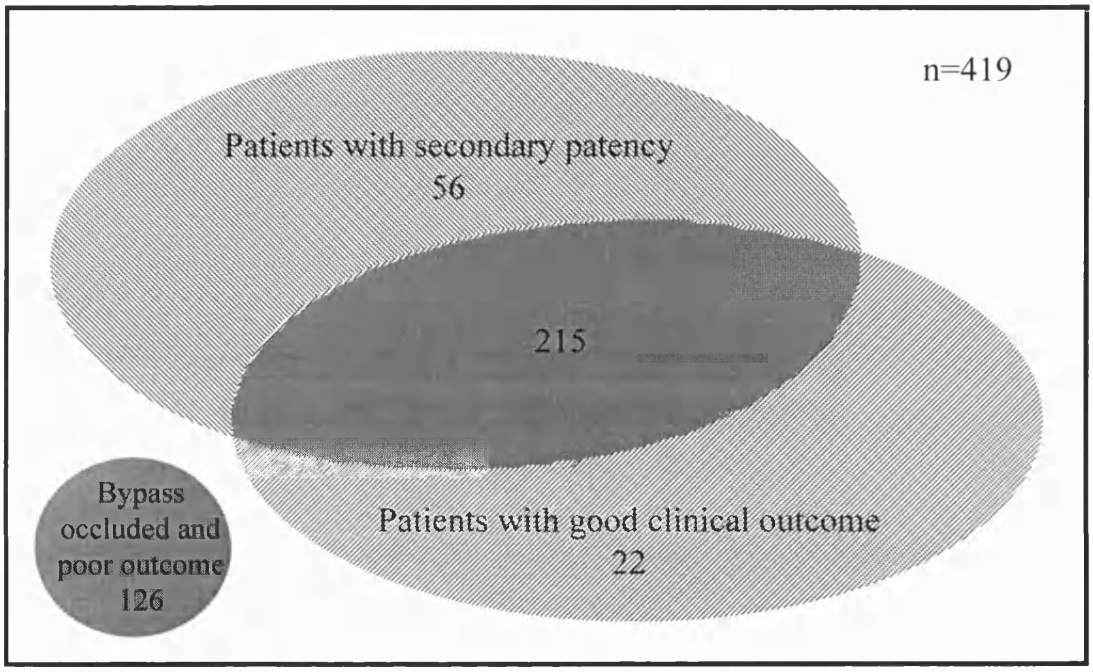


The number of false positives which would result from considering patency as a surrogate for limb survival would be 16/419 (3.8%) and the number of false negatives would be 59/49 (14.1%). In total the proportion of correct assessments would be 344/419 cases (82.1%). This confirms that bypass patency is of value as a surrogate endpoint for limb

survival in this kind of patient and bypass procedure, but the proportion of false negatives is higher than one would wish for such an endpoint.

The concordance of bypass patency with clinical outcome is shown in Figure 42. A good clinical outcome was defined as limb survival with Fontaine stage I or II and a poor outcome as amputated or limb survival with Fontaine stage III or IV.

Figure 42. Concordance of secondary bypass patency and clinical outcome at 12 months amongst patients alive and followed up. The solid shading represents the 81.4% of cases with agreement between the technical endpoint and clinical outcome.



The number of false positives which would result from considering patency as a surrogate for a good clinical outcome as defined here would be 56/419 (13.4%) and the number of false negatives would be 22/419 (5.3%). In total the proportion of correct assessments overall would be 341/419 cases (81.4%), which is similar to the concordance of patency with limb survival, but with more false positives and fewer false negatives. This confirms that secondary bypass patency is also of some value as a surrogate endpoint for clinical outcome in this kind of patient and bypass procedure, but that it is not wholly accurate as an indication of clinical success. It would be useful to present additional clinical information if patency is used as a primary trial endpoint. Primary patency, which is more commonly used as the primary efficacy variable than secondary patency, showed a slightly poorer agreement with clinical outcome.

Surrogate endpoints in some indications have been accepted by drug regulatory authorities without clinical trials demonstrating clinical benefit to the patient. Examples of

this are the licensing of blood pressure lowering agents for the treatment of hypertension and lipid-lowering agents for the treatment of hyperlipidaemias. The evidence linking blood pressure-lowering and cholesterol-lowering with reductions respectively in the incidence of stroke and myocardial infarctions and cardiovascular death is considered strong enough to justify use of such drugs before the completion of long-term studies showing clinical benefit with the agent in question, although some such agents may not produce a net benefit due to additional harmful effects (Psaty *et al* 1996, Law *et al* 1994). Other examples of surrogate endpoints in cardiovascular disease serve to illustrate the importance of having clinical endpoints before the widespread adoption of new treatments. Haemodynamic measurements and exercise tolerance in chronic heart failure are examples of surrogates which do not provide definitive evidence of clinical benefit. Drugs predicted to be useful on the basis of effects on these variables have sometimes been found to *increase* mortality, for example milrinone and flosequinan (Packer *et al* 1991 and 1993).

Ideally, clinical trials using peripheral bypass patency as a primary endpoint should show corresponding changes in patients symptoms or clinical outcomes in order to avoid being misled by results on a surrogate endpoint. Alternatives to patency as a primary endpoint could also provide a more accurate indication of the clinical outcome.

Alternative endpoints to patency

Intervention-free status was investigated as an alternative to bypass patency. No reported instance of this endpoint being used in clinical trials of adjuvant therapy was found, although numbers of interventions have been reported when comparing the use of different surgical techniques, for example by Lawson *et al* (1999). Despite the potential disadvantages of being dependent on the surgeon's judgement as to whether a further procedure is needed and feasible, this endpoint was found to be a more accurate indicator of clinical outcome than bypass patency. The rate of false positives or negatives was just under 10%, within the range suggested by Fleming *et al* (1996), as a criterion for accepting a surrogate endpoint. In this study all interventions were apparently indicated by the poor symptoms, but if this endpoint is used in future trials, this should be documented in order to increase confidence in the results.

Philosophically, patency and intervention-status are diametrically opposite approaches to obtaining information on clinical outcome. Bypass patency is presumed to be informative because it is expected to determine the clinical outcome. Interventions, on the other hand, are informative because they reflect the clinical course of the patient since the initial bypass procedure. Each approach has some merit. Successful surrogate

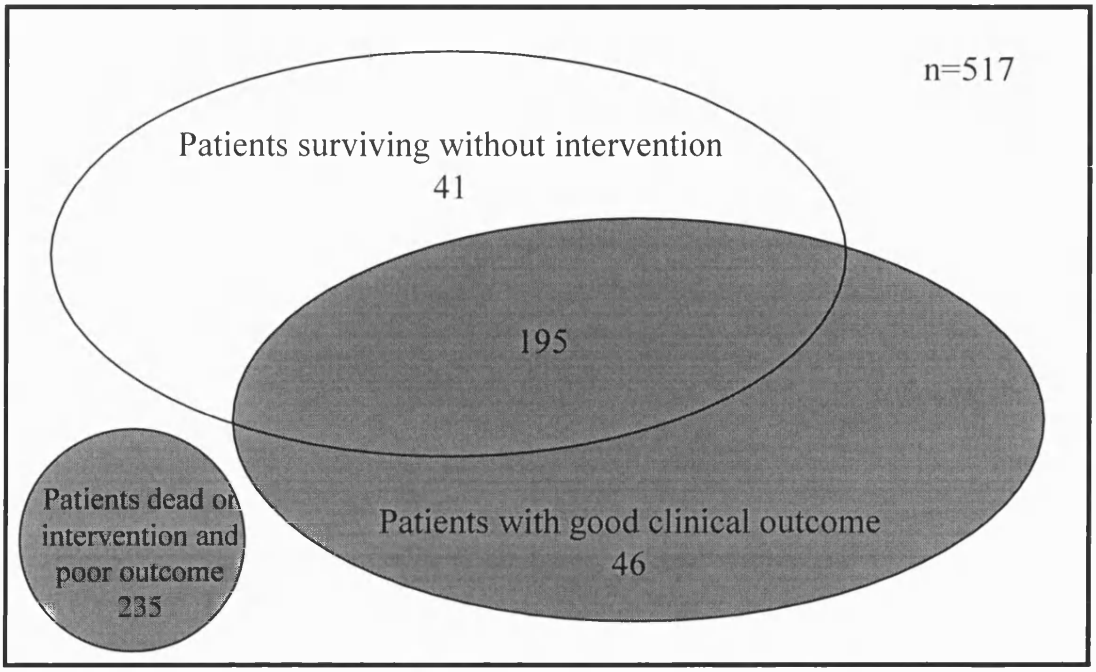
variables such as serum cholesterol and blood pressure tend to be of the former variety. The weaknesses of each approach are, firstly, that factors other than patency influence the clinical outcome and, secondly, that additional factors besides the symptoms of ischaemia will influence whether or not an intervention is performed.

As both patency and interventions are an indirect measure of clinical outcome, a more direct measure of the patients symptomatic improvement or quality of life would be ideal, but this is difficult to find. Limb survival provides important clinical information, but is too blunt a tool to be useful in most trials on patients undergoing peripheral bypass surgery, as the amputation rate will be too low in most patient groups to provide a sensitive indicator of drug effects. Typically 12 month amputation rates in vein grafts would range from about 6% in femoropopliteal grafts (Lawson *et al* 1999) to 19% in femorodistal grafts as seen in this study.

Exercise tests post-operatively are not useful in patients who are asymptomatic or in those who have pain at rest. The Fontaine classification is a single scale running from asymptomatic to severe symptoms, but is a rather crude system which does not distinguish, for example between patients with trophic lesions who have rest pain and those who have trophic lesions alone. Pain is also difficult to assess while analgesics are being taken. A symptom score such as that proposed here for pre-operative assessment of the patients might also be useful post-operatively. However, this has not been tested and the ideal score would encompass a wider range of symptom severity than could be tested in the patient group studied. Previous attempts at developing a score or more sophisticated classification of patients with PAOD have been relatively complicated to apply and have involved an element of subjectivity on the part of the patient or the clinician (Belch *et al* 1991, Rutherford *et al* 1997).

Patency and intervention-free status as endpoints both have the advantage of being objectively verifiable. Alternatives to these technical endpoints which would retain this advantage and add more clinical information would be a composite endpoint of 'survival with an intact limb and patency' or 'survival without further interventions'. Of all of the endpoints considered, 'survival without intervention' was found to be the most closely associated with clinical outcome (Figure 43). Including several aspects of the patient's outcome in a single composite endpoint has attractions in selecting a single primary trial endpoint, although it would be desirable to know in addition how each component of such a composite endpoint had changed. One example of such a composite endpoint, 'survival with an intact limb and patency', was found in an adjuvant therapy trial (Becquemin 1997), but 'survival without intervention' does not appear to have been used before.

Figure 43. Intervention-free survival showed the closest agreement with clinical symptoms of all of the objective endpoints investigated. The solid shading represents the 92.1% of cases with agreement between the intervention-free survival and the clinical symptoms.



Composite endpoints have also been advocated in the recently published guidelines on non-surgical trials in PAOD (Labs *et al* 1999). Parallels can be drawn from trials in patients with coronary artery disease in which composite endpoints are now frequently used and expert endpoint committees appointed to adjudicate all reports of endpoints before analysis of the data. A composite endpoint of death, myocardial infarction or urgent revascularisation is common in coronary intervention trials (Tcheng 1997) and widely accepted as a primary study endpoint. The individual components of the composite endpoint are usually reported as secondary endpoints in addition in order to give more information. The main weakness in this composite endpoint is probably the definition of urgent revascularisation as the criteria for deciding to intervene may be difficult to standardise. Perhaps because of this, one major recent trial in unstable coronary disease has opted for a more limited composite endpoint of death or MI (Harrington 1997).

The clinical situation after percutaneous transluminal coronary angioplasty (PTCA) is not dissimilar to that in peripheral bypass surgery. An equivalent to the PTCA composite endpoint of death, MI or coronary revascularisation would be the use of a

composite of death, amputation, bypass occlusion or intervention in peripheral bypass patients. The omission of any assessment of symptoms of leg ischaemia insufficiently severe to lead to surgical intervention would parallel the case of the patients with coronary artery disease with mildly disabling angina post-intervention. Some trials of patients with coronary disease have attempted to include an index of recurrent angina in the definition of a primary composite endpoint (PRISM study investigators 1998, PRISM-PLUS study investigators 1998), but despite the attraction of completing the clinical picture, this introduces a greater element of subjectivity which may be detrimental to the ultimate acceptability of the endpoint. A degree of subjectivity may be impossible to avoid in, for example, the criteria for the decision to intervene pre-emptively in a graft deemed to be at risk, giving rise to varying differences in rates of primary and assisted primary patency across centres.

The striving for objectivity in the endpoint has led, in the case of trials in cardiac disease, to the use of independent clinical endpoint committees which review and confirm the accuracy of the endpoint classification (Thygesen 1999). Their primary concern is the evidence for a myocardial infarction, since death and revascularisation are generally quite clear cut, but classification of causes of death is also of importance for secondary analyses. There would appear to be less of a need for such committees in peripheral vascular disease unless symptomatic assessments were to be included. Death, amputation and further interventions are quite easy for an experienced visiting monitor to identify and verify in the patient's notes. The classification of these should also rarely cause any difficulty unless it was felt necessary to classify the cause of death.

Only one trial in peripheral bypass surgery has reported using an independent expert committee to oversee endpoints serving to reduce clinician bias as well as to standardise interpretations across different surgical centres (Becquemin 1997). Unfortunately, the extent of the agreement between the investigators' and the committee's opinions were not reported. Such an arrangement may be particularly valuable in a non-blinded trial, where clinician bias should could be an issue. A risk with using an endpoint committee is that it can introduce a new variable in the form of substantial discrepancies between the results of the investigator who has seen the patient at first hand and the endpoint committee which has to rely on documented evidence (Deckers *et al* 1998, Näslund *et al* 1999). Such a situation can serve to confuse, rather than clarify the true results.

The ICH guidelines address the selection of a primary target variable for trials of new drugs, recommending that it should be 'the variable capable of providing the most clinically relevant and convincing evidence directly related to the objective of the trial'.

This points to the selection of the intervention-free status either alone or in combination with patient survival rather than bypass patency in future studies. However, the guidelines go on to recommend that it should also be 'a reliable and validated variable with which experience has been gained either in earlier studies or in the published literature' and that it should 'reflect the accepted norms and standards in the relevant field of research' (ICH Expert Working Group 1997 and 1998). Bypass patency is clearly the accepted norm at present, so it may be that further studies will have to provide evidence for the greater clinical value of reporting interventions before it is likely to be adopted as a primary endpoint for important efficacy studies.

The iloprost study only included patients with severe ischaemia and distal bypass grafts. The next stage in assessing the usefulness of interventions as an endpoint might be to repeat the kind of analysis performed here in patients with less severe limb ischaemia and those undergoing femoropopliteal bypass.

There is one major additional advantage of providing the absolute number of patients who are 'alive with an intact limb and patent bypass' or 'alive without further intervention'. These endpoints lend themselves readily to analysis according to the intention to treat principle as there will be no censoring due to death or amputation prior to loss of patency or intervention. A recent review has reported that the intention to treat strategy is often quoted in clinical papers, whilst clearly being interpreted in different ways (Hollis *et al* 1999). The convention in vascular surgery is to analyse patency data by life-table methods assuming that patients with missing observations would have behaved in the same way as those observed, i.e. this assumes that data are missing at random. However, this is likely to lead to bias (Choi *et al* 1995) and it has been shown that absence of patency data in one femorodistal bypass series was not independent of the outcome (Jensen *et al* 1996). If life-table analysis of patency continues to be the method choice, it would be of great value to report one of the suggested composite endpoints in addition. The ICH guidelines on the choice of a primary endpoint recommend that it should be a single variable, but do also allow for the possibility of a composite endpoint resulting from the summation or other combination of several variables or discrete categories of event provided that it is well-defined *a priori.*

Disease severity as an outcome measure

The lack of a suitable scale of disease or symptom severity has been discussed with respect to patient characterisation. The same arguments apply in the assessment of improvement in symptoms. The Fontaine classification is only able to show large changes in symptoms. A symptom score such as that used here for the pre-operative

characterisation of the patients may also be useful post-operatively and would provide a more precise measurement of severity than that offered by the Fontaine classification.

Another version of the composite endpoints discussed earlier has been proposed for non-surgical trials, in which the number of 'optimal response days' could be counted (Labs *et al* 1999). An 'optimal response day' could be defined by relief of clinical symptoms in addition to survival without amputation. Such an approach could be adapted to peripheral bypass trials and incorporate freedom from re-intervention. Unfortunately, such analysis had not been foreseen when this study was designed and the data collected did not allow such an analysis to be performed retrospectively. It would be of considerable interest to test the feasibility of such an approach.

An alternative approach would be the assessment of quality of life after bypass surgery. There is some evidence for the usefulness of a widely accepted, non-disease specific quality of life questionnaire (SF36) in demonstrating improvement following infrainguinal reconstruction (Chetter *et al* 1998, Seabrook *et al* 1999), but this might not be sensitive enough to detect postoperative treatment differences in a clinical trial. A disease specific questionnaire would be preferable. A German language 86-item quality of life scale specifically for PAOD has been developed including questions on symptoms, functional status and psychological evaluation (Bullinger *et al* 1996), but the use of this scale in peripheral bypass studies has not so far been published. Other appropriate scales are being developed (Beattie *et al* 1997) and these could also prove to be useful tools in investigating the clinical outcome of distal bypass surgery.

Patient management

There were two important issues of patient management which were left to the policy of the surgical centre in the iloprost trial: graft surveillance and post-operative antithrombotic treatment.

Surveillance of grafts for development of stenoses was performed in most of the study centres, but with widely varying detection rates only partly explained by the variation in composition of the patient populations and the type of procedures performed. The overall stenosis detection rate of 27% was comparable to the literature (Golledge *et al* 1996), but elective interventions to dilate the stenosis seldom followed and therefore had little impact on the primary patency rates as such interventions were rarely the sole reason for loss of primary patency. It had been feared that frequent intervention prior to occlusion of the graft might compromise the interpretation of primary graft patency as a primary endpoint in the trial, but this was sufficiently infrequent not to be considered a

problem. This issue could be simplified in future trials by having agreed criteria for intervening to dilate a stenosis.

A beneficial effect of aspirin on clinical outcome is beyond dispute (Antiplatelet Trialists' Collaboration 1994b). However, its use as long-term antithrombotic treatment in the iloprost study was not stipulated in the protocol as some centres, notably those in the Netherlands, prefer to use oral anticoagulants as a routine antithrombotic therapy. The use of aspirin was found to vary greatly between centres potentially posing a problem for trial interpretation. Both aspirin and oral anticoagulant use were strongly associated with an improved clinical outcome in the iloprost trial. This was a weakness in the trial design and future trials of short term therapies should probably stipulate the use of one of these treatments up to the end of the follow-up. A recently completed, but still unpublished, trial may answer the question of the relative merits of these two treatments after peripheral bypass surgery (Tangelder *et al* 1996) .

Repeat randomisation

It was found to be common practice amongst published studies in this field to count the outcome of each graft in a trial instead of each patient and thus to include some patients more than once if grafts were performed in different legs or if a second graft was performed after failure (i.e. an endpoint) had occurred in the first graft. This was done either by randomising each graft procedure separately or by randomising a patient once and counting each graft as a separate outcome in that treatment group. This can give misleading information as conventional statistical tests assume that the outcome in each case will be independent of the outcome in any other case. Knowing for example that the sex of the patient can influence the outcome, tells us that two grafts in the same patient will be subject to a common factor influencing the outcome. Other patient specific characteristics such as lifestyle, compliance with antithrombotic medication, presence of distal disease, plasma fibrinogen and blood viscosity may also link the outcome in the two grafts.

Graft or procedure specific influences on outcome such as graft material and vein quality would appear to be less important in this respect, but even these may be consistent in different procedures in the same patient. A patient who has inadequate vein for one procedure is likely still to have inadequate vein for the second. Thus a poor outcome for one graft in a patient might be strongly associated with poor outcome of a second procedure.

This problem is not unique to trials in peripheral bypass surgery. It has been observed and reported to be common in publications of ophthalmological studies in which

results of both eyes from the same patient are sometimes included in the analysis, invalidating the statistical assumptions (Newcombe *et al* 1987, Katz 1988). This is analogous to the practice of including two legs or grafts from the same patient in peripheral bypass surgery.

Future studies

The recommendations for improved study designs could be usefully applied to some agents in current clinical use. Although widely used with all types of graft material, it is far from clear that aspirin is effective in maintaining the patency of vein grafts. Oral anticoagulants have yet to be tested in a trial with a fixed duration follow-up, clear patient definition and adequate measures to eliminate bias in the assessment of patency. There is some evidence for their use in vein grafts, but none in prosthetic grafts. Ticlopidine has been shown to be effective in vein grafts in one of the few well-designed trials, but this should be confirmed and a comparison with aspirin is needed.

The evidence for a reduction in cardiovascular death and morbidity by aspirin poses an ethical dilemma in performing placebo-controlled trials. Aspirin is probably of value in all patients undergoing peripheral bypass surgery as they will be at risk, not only of graft thrombosis, but also of coronary or cerebrovascular thrombosis. There will be some patients who are intolerant of aspirin, but these may be too few for an adequately sized clinical trial to be performed. This points to a need to test other antithrombotic agents against aspirin, or a combination of the new agents plus aspirin against aspirin alone. There is potentially added value in this approach as two platelet inhibitors working by different mechanisms may have an additive or even a synergistic effect when used in combination. This has been shown with ticlopidine (Thebault *et al* 1977) and with some of the orally bioavailable platelet glycoprotein IIb/IIIa antagonists (GPIIb/IIIa antagonists) currently in development for thrombotic indications (Keriakes *et al* 1997, Theroux *et al* 1998).

Although there is a paucity of convincing trial data available, there are a number of agents which would seem to merit further investigation. As suggested in the previous paragraph, aspirin, oral anticoagulants and ticlopidine all need further studies. The data on low molecular weight heparins are also promising, but stem from open or single blind studies. Double blind trials with these subcutaneously administered drugs have been performed in other indications (Cohen *et al* 1997, FRISC-II investigators 1999) and should be performed in patients undergoing peripheral bypass procedures. Other antithrombotic agents such as clopidogrel, which inhibits ADP-induced platelet aggregation like ticlopidine, but with a better safety profile (Coukell *et al* 1997), and the aforementioned

GPIIb/IIIa antagonists which antagonise the fibrinogen-binding receptor on the platelet surface, the final common pathway in platelet aggregation to any stimulus, have potential in this indication and should be investigated in well-designed trials.

The majority of interest up till now has been in the development of antithrombotic agents for this indication. However, graft stenosis is a major contributing cause of graft occlusion and none of the agents currently available have been shown to influence this process. A compound which did so could be very valuable and current interest is centred on antagonists of the $\alpha_v\beta_3$ receptor which is thought to be important in this process (Bishop *et al* 1999) and matrix metalloproteinase inhibitors. In principle, trials of such agents would follow the same design as those of antithrombotic drugs with particular emphasis on the standardisation of the assessment of stenosis, probably by duplex ultrasound. Although the majority of stenoses occur in the first year, a slightly longer follow-up of 18 months might be appropriate.

Some years have elapsed since the planning and conduct of the iloprost trial and it was noted in the literature review of trials of adjuvant therapy that there was some evidence of improvement in trial design since the iloprost trial was initiated. However, many of the deficiencies in trial design identified have yet to be routinely addressed. Further improvements are needed in order to enable clinicians to make decisions on the optimal treatments for maintaining peripheral bypass graft patency and improving the clinical outcome in these patients.

6. CONCLUSIONS AND RECOMMENDATIONS

Conclusions and recommendations

- Published studies of adjuvant medical therapy in peripheral bypass surgery frequently have weaknesses in study design and patient selection, and most notably in the reporting of clinical outcomes.
- A multicentre trial demonstrated a general lack of effect of peri-operative iloprost on bypass patency and clinical endpoints when used in patients undergoing femorodistal bypass procedures. An absolute increase of 12.5% in the primary patency rate of femrodistal vein grafts with iloprost could be excluded.
- A simple symptom severity score was used which could be more useful than the Fontaine classification for describing a study population with severe PAOD, as it was shown to be strongly associated with the clinical outcome in terms of 'limb survival', 'patient survival' and 'patient survival with an intact limb and patent graft'.
- Patient selection is important and possible interactions between the adjuvant treatment and characteristics of the patients or operations should be taken into account when planning a study. An example of this is the importance of differentiating between vein and prosthetic graft materials which was illustrated by the meta-analysis of outcomes of published studies with aspirin and sulphinpyrazone.
- The comparison of different centres in the iloprost trial indicated that the selection of patients for this type of operation may vary significantly between centres even when following a common protocol, particularly in terms of disease severity.
- The intercentre differences identified did not appear to have played a major role in the iloprost study as the outcome was similar in most centres. However, intercentre differences in graft stenosis rates could have implications for trials of drugs designed to act on stenosis development.
- Studies requiring strict consistency in patient selection, procedures and postoperative management may be best performed in single centres, but most studies will require the cooperation of more centres in order to achieve the desired numbers of cases. In this case careful definitions of policy should be adhered to. Data on a centre's recent results and data on patients not included during a trial will help to assess the impact of the selection criteria in a study. Another approach in the absence of adequate multicentre trials is to use meta-analysis and identify sources of heterogeneity.
- Bypass patency is of value as a surrogate endpoint for limb survival and clinical improvement of clinical symptoms in patients undergoing femorodistal bypass surgery, but the number of false negatives and false positives is sufficient to warrant the reporting of additional clinical results.

- An alternative technical endpoint to bypass patency is the intervention-free status of the patient. In these investigations, intervention-free status was found to represent clinical improvement more accurately than bypass patency. The value of this endpoint should be investigated further in other types of patients and procedures.
- Composite endpoints deserve consideration as primary endpoints in clinical trials in this field. They can incorporate both technical and clinical outcome measures and arguably provide the best overall measure of success in addition to lending themselves well to intention-to-treat analysis.
- The need to obtain agreement on strict protocols covering surgical procedures and criteria for patient selection and intervention makes performing large multicentre trials difficult in this indication. An alternative is to use meta-analysis techniques to analyse data from several smaller trials, but sensible investigation of sources of heterogeneity should be included.

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APPENDIX I

List of abbreviations

Abbreviations listed below are those appearing in the text. Additional abbreviations may be used in some tables and these are explained in footnotes to the relevant tables.

Abbreviation	Explanation
ABPI	Ankle-brachial pressure index
ASA	Acetylsalicylic acid, aspirin
CABG	Coronary artery bypass graft
CLI	Critical limb ischaemia
CRF	Case report form
CVA	Cerebrovascular accident (used as a synonym for stroke)
DSA	Digital subtraction angiography
GCP	Good Clinical Practice
GP IIb/IIIa	Platelet glycoprotein IIb/IIIa
HUV	Human umbilical vein
ICH	International Conference on Harmonisation of GCP
LMWH	Low molecular weight heparin
MI	Myocardial infarction
PAOD	Peripheral arterial occlusive disease
PGE_1	Prostaglandin E_1
PGI_2	Prostaglandin I_2, prostacyclin
PSV	Peak systolic velocity
PTA	Percutaneous transluminal angioplasty
PTCA	Percutaneous transluminal coronary angioplasty
PTFE	Polytetrafluoroethylene (a prosthetic graft material)
SDV	Source data verification
SFA	Superficial femoral artery
TEA	Thromboendarterectomy
TIA	Transient ischaemic attack
TxA_2	Thromboxane A_2
UFH	Unfractionated heparin
V_2/V_1	Velocity ratio
5-HT	5-hydroxytryptamine (serotonin)

APPENDIX II

Publications derived from this thesis

Iloprost Bypass International Study group *(corresponding author H.R.Watson).*
Effects of iloprost on patency of femorodistal bypass grafts.
Eur J Vasc Endovasc Surg 1996; **12**: 301-306

Watson HR, Schroeder TV, Simms MH, Buth J, Horrocks M, Norgren L, Bergqvist D.
Relationship of clinical outcome to patency of femorodistal bypass grafts.
Eur J Vasc Endovasc Surg 1999; **17**: 77-83

Watson HR, Belcher G, Horrocks M.
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Br J Surg 1999; **86**: 981-991

Watson HR, Skene AM, Belcher G.
Graft material and results of platelet inhibitor trials in peripheral arterial reconstructions: reappraisal of results from a meta-analysis.
Br J Clin Pharmacol 2000; **49**: 191-195

Publications derived from this thesis and currently in press

Watson HR, Schroeder TV, Simms MH, Horrocks M.
Association of sex with patency of femorodistal bypass grafts.
Eur J Vasc Endovasc Surg *(in press)*

Watson HR, Schroeder TV, Simms MH, Buth J Horrocks M.
Incidence of stenoses in femorodistal bypass vein grafts in a multicentre study.
Eur J Vasc Endovasc Surg *(in press)*

Relevant publications by the author on studies preceding this thesis

Hickey NC, Shearman CP, Crowson MC, Simms MH, Watson HR
Iloprost improves femorodistal graft flow after a single bolus injection
Eur J Vasc Surg 1991; **5**: 19-22

Smith FCT, Hildebrand M, Watson HR, Shearman CP
Pharmacokinetics of intragraft iloprost infusion during femorocrural reconstruction
In: Agents and Actions Supplement 37: Prostaglandins in the Cardiovascular System, Ed. Sinzinger and Schroer (1992), Birkhaeuser, Basel. Pages 66-70

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Iloprost reduces peripheral resistance during femorodistal reconstruction
Eur J Vasc Surg 1992; **6**: 194-198

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